Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	39	(zidovudine or azt or retrovir) with conjugat$ and @pd>"20040308"	US-PGPUB; USPAT	OR	ON	2005/04/07 12:19
L2	24	((zidovudine or azt or retrovir$) with (pro! adj drug or pro$1drug$1)) and ((514/2-21). ccls. or "530"/$.ccls.) and @pd>"20040308"	US-PGPUB; USPAT	OR	ON	2005/04/07 12:23
L3	1240	((zidovudine or azt or retrovir$) with (sidechain or amino adj acid or peptide or polypeptide or protein)) and ((514/2-21).ccls. or "530"/$.ccls.) and @pd>"20040308"	US-PGPUB; USPAT	OR	ON	2005/04/07 12:22
L4	1158	((zidovudine or azt or retrovir$) with (side$1chain or side adj chain or amino adj acid or protein or polypeptide)) and ((514/2-21). ccls. or "530"/$.ccls.) and @pd>"20040308"	US-PGPUB; USPAT	OR	ON	2005/04/07 12:24
L5	40	((zidovudine or azt or retrovir) with (side$1chain$1 or side adj chain or amino adj acid or protein or polypeptide)) and ((514/2-21). ccls. or "530"/$.ccls.) and @pd>"20040308"	US-PGPUB; USPAT	OR	ON	2005/04/07 12:27
L6	83	(zidovudine or azt or retrovir) with (di$1peptide$1 or glutamic or glu! or lys! or lysine or glutamyl or lysinyl)	US-PGPUB; USPAT	OR	ON	2005/04/07 12:33
L7	17	(zidovudine or azt or retrovir) with (di$1peptide$1 or glutamic or glu! or lys! or lysine or glutamyl or lysinyl)	EPO; JPO; DERWENT	OR	ON	2005/04/07 12:33

Checked L4, L2, L5, L6, L7

JR

4-7-2005

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Set     Items   Description
S1      22126   ZIDOVUDINE OR AZT OR RETROVIR
S2     299348   DIPEPTIDE?? OR GLUTAMIC OR GLUTAMYL OR GLU OR LYSINE OR LY-
            SINYL OR LYS
S3        161   S1 AND S2
S4        141   S3 NOT (PY=2005 OR PY=2004 OR PY=2003 OR PY=2002 OR PC=US -
            OR PC=EP OR PC=WO)
S5         99   RD S4 (unique items)
?
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B 155,5.399

Checked S5

JSR

4-7-2005

ACCESS DB # 149235

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Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: Jeffrey E. Russel Examiner # : 62785 Date: 3-29-2005
Art Unit: 1654 Phone Number: 2-0969 Serial Number: 09/933,748
Location (Bldg/Room#): REM 3019 (Mailbox #): 3C18 Results Format Preferred (circle): PAPER DISK

****

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: Active Agent Delivery Systems

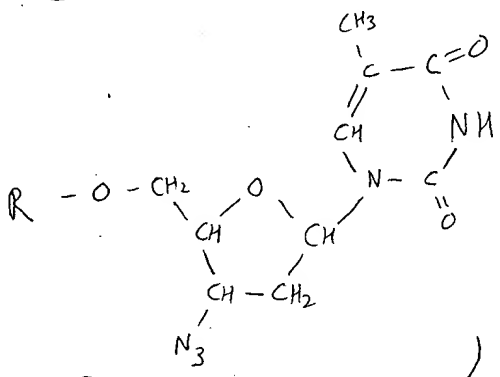
Inventors (please provide full names): T. Piccariello, L. Olon, R. Kirk

Earliest Priority Date: 8-22-2001

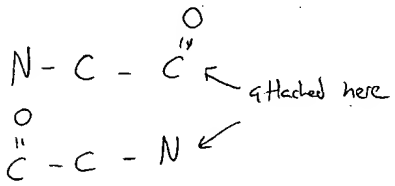
Search Topic:
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

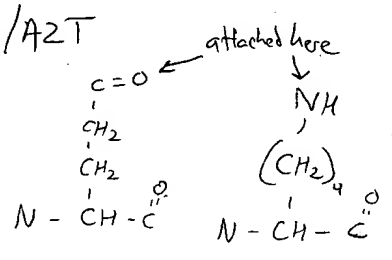
For Sequence Searches Only ***Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.***

Please search the following partial structures:



Zidovudine/AZT

Where R = 



Thank you. JER

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STAFF USE ONLY

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Searcher Phone #: _____
Searcher Location: _____
Date Searcher Picked Up: _____
Date Completed: _____
Searcher Prep & Review Time: _____
Online Time: _____

Type of Search

_____ NA Sequence (#)
_____ AA Sequence (#)
_____ Structure (#)
_____ Bibliographic
_____ Litigation
_____ Fulltext
_____ Other

Vendors and cost where applicable

_____ STN _____ Dialog
_____ Questel/Orbit _____ Lexis/Nexis
_____ Westlaw _____ WWW/Internet
____ In-house sequence systems
___ Commercial ___ Oligomer ____ Score/Length
___ Interference ___ SPDI ____ Encode/Transl
_____ Other (specify)

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=> d his ful

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L1             31 SEA ABB=ON  ("PICCARIELLO T"/AU OR "PICCARIELLO THOMAS"/AU OR
                  "PICCARIELLO TOM"/AU)
                  E OLON LAWRENCE P/AU
L2              8 SEA ABB=ON  ("OLON LAWRENCE P"/AU OR "OLON LAWRENCE PETER"/AU)
                  E KIRK RANDAL J/AU
L3             10 SEA ABB=ON  ("KIRK RANDAL J"/AU OR "KIRK RANDALL J"/AU)
L4              6 SEA ABB=ON  L1 AND L2 AND L3
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                  DELETE SELECT
                  SELECT RN L4 2-3

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                  I OR 86409-29-2/BI OR 93594-48-0/BI)

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L6              6 SEA ABB=ON  L4 AND L5

     FILE 'REGISTRY' ENTERED AT 17:24:20 ON 06 APR 2005
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                  E ZIDOVUDINE AZT/CN
L7              1 SEA ABB=ON  "ZIDOVUDINE AZIDO REDUCTASE"/CN
                  E ZIDOVUDINE/CN
L8              1 SEA ABB=ON  ZIDOVUDINE/CN
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L9 STRUCTURE 30516-87-1
L10 5 SEA SSS SAM L9
L11 64 SEA SSS FUL L9 64 compds in Reg. - see "d que stat"

FILE 'HCAPLUS' ENTERED AT 17:31:32 ON 06 APR 2005
L12 37 SEA ABB=ON L11 37 cits from CAPlus

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=> d que stat l12
L9                  STR
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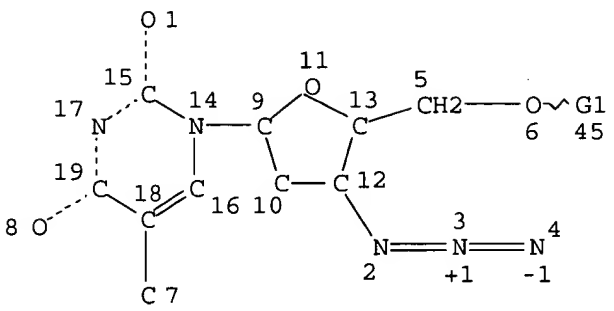

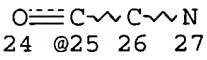

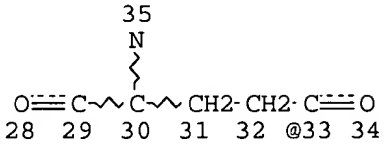

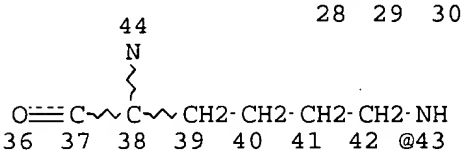


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CHARGE  IS E+1    AT   3
CHARGE  IS E-1    AT   4
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  45

STEREO ATTRIBUTES: NONE
L11          64 SEA FILE=REGISTRY SSS FUL L9
L12          37 SEA FILE=HCAPLUS ABB=ON  L11
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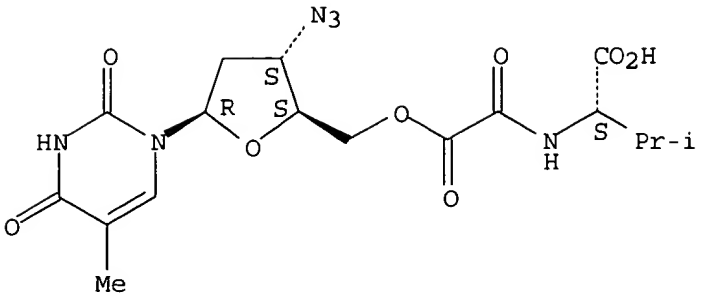
L12 ANSWER 1 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:410478 HCAPLUS
DOCUMENT NUMBER: 142:156248
TITLE: Electronic structure of some antiviral compounds
AUTHOR(S): Giambasu, Madalin G.; Diaconu, Carmen C.; Hillebrand, Mihaela
CORPORATE SOURCE: Dep. Phys. Chem., Fac. Chem., Univ. Bucharest, Bucharest, Rom.
SOURCE: Internet Electronic Journal of Molecular Design (2004), 3(2), 73-82
CODEN: IEJMAT; ISSN: 1538-6414
URL: http://www.biochempress.com/av03_0073.html
PUBLISHER: BioChem Press
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB As a first step in a theor. approach on the multidrug resistance (MDR) process occurring during long-time therapy with antiviral and antitumoral drugs and the mol. modeling of the interaction of the drugs with the P-Glycoprotein (P-gp) overexpressed in these cases, we have investigated the electronic structure of some antiviral compds., Zidovudine (AZT), 3'-azido-3'-deoxy-5'-O-oxalylthymidine acid (AZT-Ac), 3'-azido-3'-deoxy-5'-O-oxalyl-N-valinethymidine (AZT-Val3) and 3-azido-3'-deoxy-5-O-iso-nicotinoyl-thymidine (AZT-Iso4). The calcns. were performed by semiempirical, AMI, and ab initio 6-31G* methods using the AMSOL and GAMESS programs. A conformational search considering the most significant torsions was previously made using the Hyperchem program and the lowest energy conformers were further subject to a fully optimization in octanol, model for a nonpolar solvent and water. To establish the position of the azide group in respect with the ribose cycle, the potential energy surface was built, considering as coordinate the torsion about the ribose-azide bond. The solvation effects in the ab initio method were treated in the frame of the self-consistent reaction field (SCRF). For all the compds., the conformational search revealed similar relative positions of the thymine and ribose ring, slightly influenced by the solvent. Concerning the azide group the semiempirical results were drastically changed in going from in vacuo to water optimizations. A strongly stabilized solvated species, with a different charge distribution than in vacuo was evidenced in water. The calculated free energies of solvation are larger in water in comparison with octanol, excepting compound 3 for which the difference is small in agreement with its larger expected lipophilicity. The solvation effects predicted by the ab initio method are smaller. The essential change in the electronic charge distribution of the azide nitrogens in water in comparison to in vacuo calcns. shows that in order to have a correct estimation of the electrostatic contributions in the modeling of protein-AZT derivs. interaction the solvation processes must be taken into account.

IT **395089-95-9**
RL: CPS (Chemical process); FMU (Formation, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); FORM (Formation, nonpreparative); PROC (Process)
(electronic structure potential energy surface conformational anal. of substituted AZT nucleoside analogs)

RN 395089-95-9 HCAPLUS
CN L-Valine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:269853 HCAPLUS
DOCUMENT NUMBER: 140:309370
TITLE: Amino acid and peptide carriers for oral delivery of active agent
INVENTOR(S): Piccariello, Thomas; Kirk, Randal J.; Olon, Lawrence P.
PATENT ASSIGNEE(S): New River Pharmaceuticals Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 176 pp., Cont.-in-part of U.S. Pat. Appl. 2002 128,177.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004063628	A1	20040401	US 2002-156527	20020529
WO 2000052078	A1	20000908	WO 2000-US5693	20000306
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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US 6716452	B1	20040406	US 2000-642820	20000822
US 2002128177	A1	20020912	US 2001-986426	20011108
WO 2003072047	A2	20030904	WO 2003-US5526	20030224
WO 2003072047	A3	20040617		
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CA 2477088 AA 20031002 CA 2003-2477088 20030224
WO 2003079972 A2 20031002 WO 2003-US5524 20030224
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EP 1490090 A2 20041229 EP 2003-713634 20030224
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WO 2003101476 A1 20031211 WO 2003-US17009 20030529
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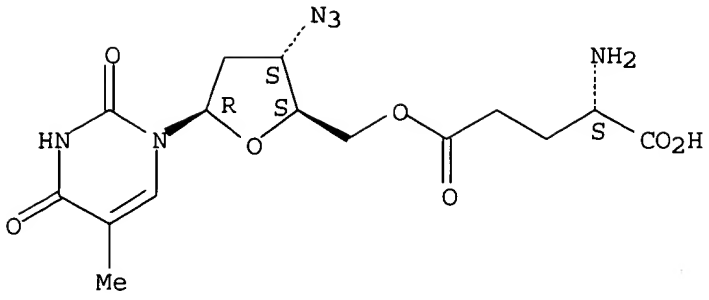
US 2004127397 A1 20040701 US 2003-727565 20031205
PRIORITY APPLN. INFO.: US 1999-265415 B2 19990310
US 1999-411238 B2 19991004
WO 2000-US5693 A 20000306
US 2000-642820 A2 20000822
US 2001-986426 A2 20011108
US 1999-123146P P 19990305
US 2002-358381P P 20020222
US 2002-366258P P 20020322
US 2002-136433 A 20020502
US 2002-156527 A 20020529
WO 2003-US5524 W 20030224

AB The present invention relates to oral delivery systems of active agent, and more specifically to compns. that comprise amino acids, as single amino acids or peptides, covalently attached to active agents and methods for oral administration of conjugated active agent compns. For example, a polyserine-furosemide conjugate was prepared and its in vivo performance was examined Compared to parent furosemide, the conjugate showed a sustained drug release. The 9 h serum level of the polyserine-furosemide conjugate was 95.5% of its 3 h level, whereas the 9 h serum level of the parent drug was only 59.8% of its 3 h level.

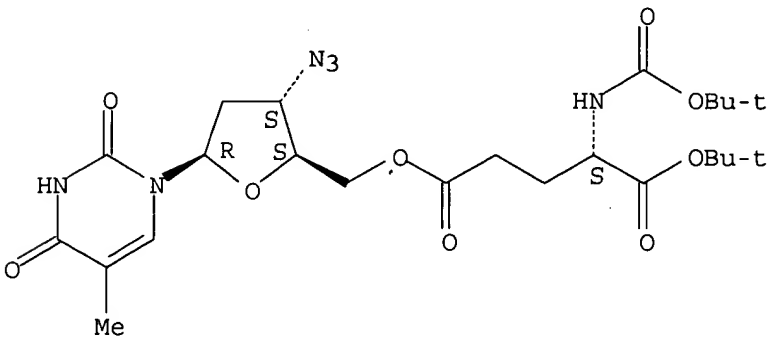
IT **125780-86-1P**
RL: PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates containing amino acid or peptide carriers for sustained-release oral drug delivery)
RN 125780-86-1 HCAPLUS
CN L-Glutamic acid, 5→5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **125780-85-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(conjugates containing amino acid or peptide carriers for sustained-release oral drug delivery)
RN 125780-85-0 HCAPLUS
CN L-Glutamic acid, N-[(1,1-dimethylethoxy)carbonyl]-, 1-(1,1-dimethylethyl) ester, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



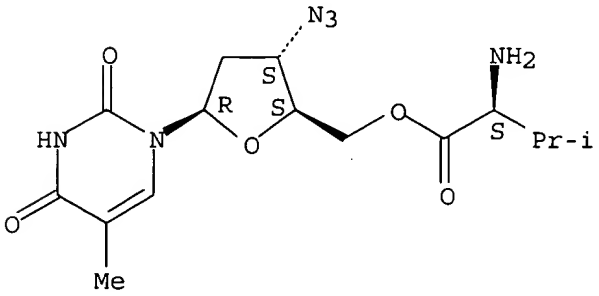
L12 ANSWER 3 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:125182 HCAPLUS
DOCUMENT NUMBER: 141:136076
TITLE: A Novel Nucleoside Prodrug-Activating Enzyme: Substrate Specificity of Biphenyl Hydrolase-like Protein
AUTHOR(S): Kim, Insook; Song, Xueqin; Vig, Balvinder S.; Mittal, Sachin; Shin, Ho-Chul; Lorenzi, Philip J.; Amidon, Gordon L.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, College of Pharmacy, The University of Michigan, Ann Arbor, MI, 48109-1065, USA
SOURCE: Molecular Pharmaceutics (2004), 1(2), 117-127
CODEN: MPOHBP; ISSN: 1543-8384
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Biphenyl hydrolase-like protein (BPHL, NCBI accession number NP-004323) is a novel human serine hydrolase recently identified as a human valacyclovirase, catalyzing the hydrolytic activation of the antiviral prodrugs valacyclovir and valganciclovir. The substrate specificity of

BPHL was investigated with a series of amino acid ester prodrugs of the therapeutic nucleoside analogs: acyclovir, zidovudine, floxuridine, 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl) benzimidazole, and gemcitabine. The hydrolysis of typical esterase and aminopeptidase substrates by BPHL was also investigated. The results indicate that the substrate specificity of BPHL is largely determined by the amino acid acyl promoiety, and is less sensitive to the nucleoside parent drugs. For all nucleoside parent drugs, BPHL preferred the hydrophobic amino acids valine, phenylalanine, and proline over the charged amino acids lysine and aspartic acid. The position and monoester or diester form of the prodrug were also important, with BPHL exhibiting higher affinity for the 5'-esters than for the 3'-esters and the 3',5'-diesters irresp. of amino acid type. Further, the presence of the 3'-amino acid ester considerably reduced the hydrolysis rate of the 5'-amino acid ester functionality. BPHL exhibited stereoselectivity with an L/D specificity ratio of 32 for 5'-valyl floxuridine and 1.5 for 5'-phenylalanyl floxuridine. The substrate specificity suggests that the substrate-binding pocket of BPHL has a hydrophobic acyl binding site which can accommodate the pos. charged α-amino group, while having an alc. leaving group binding site that can accommodate nucleoside analogs with a relatively generous spatial allowance. In conclusion, BPHL catalyzes the hydrolytic activation of amino acid esters of a broad range of therapeutic nucleoside analogs in addition to valacyclovir and valganciclovir and has considerable potential for utilization as an activation target for design of antiviral and anticancer nucleoside analog prodrugs.

IT **128305-57-7**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(substrate specificity and structural requirements of biphenyl hydrolase-like protein, a human valacyclovirase, for amino acid esters of nucleoside prodrugs)

RN 128305-57-7 HCAPLUS
CN L-Valine, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:971909 HCAPLUS
DOCUMENT NUMBER: 140:16982
TITLE: Peptide conjugates for protecting and administering active agents
INVENTOR(S): Piccariello, Thomas; Kirk, Randal J.; Olon, Lawrence P.
PATENT ASSIGNEE(S): New River Pharmaceuticals Inc., USA

SOURCE: PCT Int. Appl., 161 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

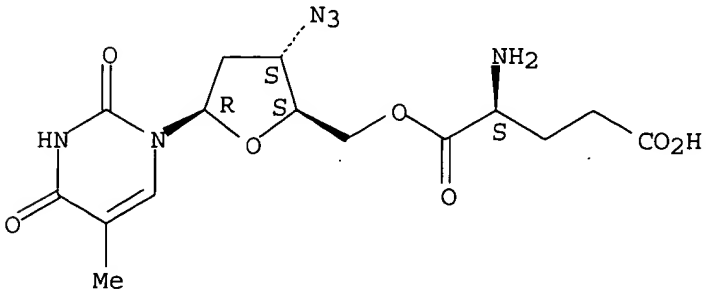
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003101476	A1	20031211	WO 2003-US17009	20030529
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004063628	A1	20040401	US 2002-156527	20020529
PRIORITY APPLN. INFO.:			US 2002-156527	A 20020529
			US 1999-265415	B2 19990310
			US 1999-411238	B2 19991004
			WO 2000-US5693	A 20000306
			US 2000-642820	A2 20000822
			US 2001-986426	A2 20011108

AB The invention relates to active agent delivery systems and more specifically to compns. that comprise amino acids, as single amino acids or peptides, covalently attached to active agents and methods for administering conjugated active agent compns. E.g., poly(glutamic acid) was linked to a number of active agents such as cephalexin and atenolol. In vitro and in vivo performance studies were carried out such as caco-2 human intestinal epithelia cell studies which indicated the conjugates enhance oral delivery.

IT **607706-93-4P 607706-98-9P 607706-99-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(peptide conjugates for protecting and administering active agents)

RN 607706-93-4 HCAPLUS
CN L-Glutamic acid, (1→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

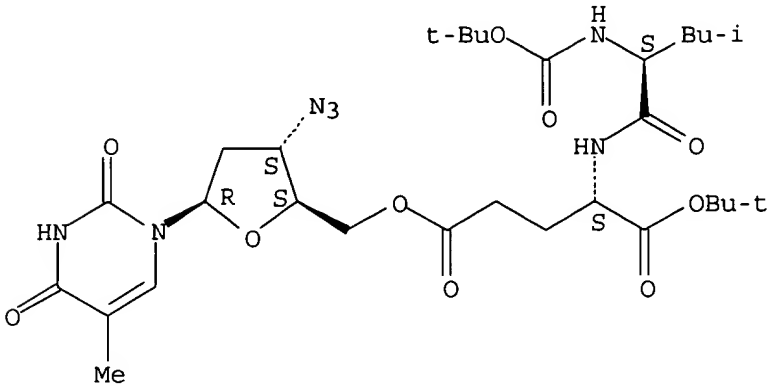
Absolute stereochemistry.



RN 607706-98-9 HCAPLUS
CN L-Glutamic acid, N-[(1,1-dimethylethoxy)carbonyl]-L-leucyl-,

21-(1,1-dimethylethyl) ester, (25→5')-ester with
3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

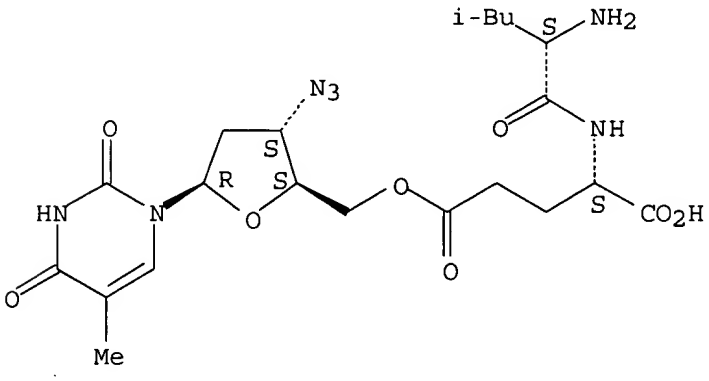


RN 607706-99-0 HCAPLUS
CN L-Glutamic acid, L-leucyl-, (25→5')-ester with 3'-azido-3'-deoxythymidine, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

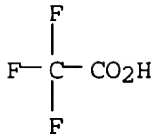
CRN 607706-97-8
CMF C21 H31 N7 O8

Absolute stereochemistry.



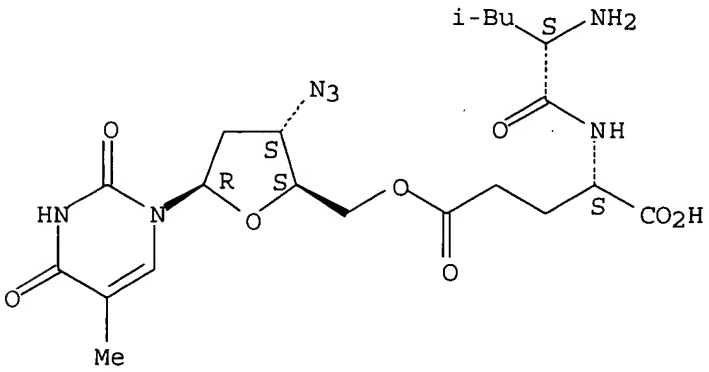
CM 2

CRN 76-05-1
CMF C2 H F3 O2



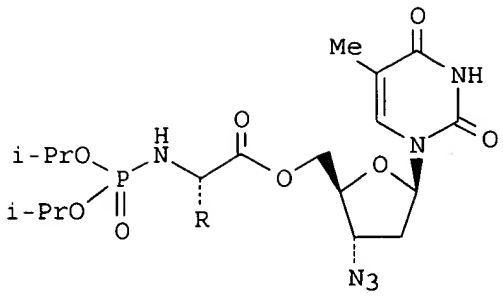
IT **607706-97-8P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(peptide conjugates for protecting and administering active agents)
RN 607706-97-8 HCAPLUS
CN L-Glutamic acid, L-leucyl-, (25→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:835475 HCAPLUS
DOCUMENT NUMBER: 140:164119
TITLE: Characteristic fragmentation behavior of phosphoamino acid conjugates with 3'-azido-3'-deoxythymidine by electrospray ionization tandem mass spectrometry
AUTHOR(S): Xiao, Qiang; Ju, Yong; Zhao, Yufen; Cui, Yuxin
CORPORATE SOURCE: The Key Laboratory of Bioorganic Phosphorus Chemistry, Ministry of Education, Department of Chemistry, School of Life Sciences and Engineering, Tsinghua University, Beijing, 100084, Peop. Rep. China
SOURCE: Rapid Communications in Mass Spectrometry (2003), 17(20), 2273-2278
CODEN: RCMSEF; ISSN: 0951-4198
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



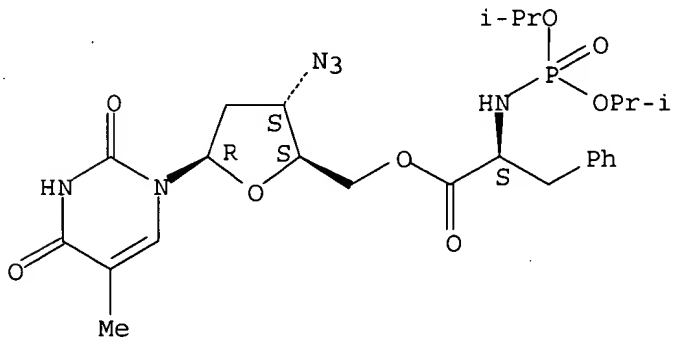
I

AB The conjugates I (R = CH2Ph, Me, CHMe2, CH2CHMe2) of phosphoamino acids with 3'-azido-3'-deoxythymidine were synthesized and their structures were determined by various spectral methods. In pos. and neg. ion electrospray mass spectrometry (ESI-MS), the fragmentation pathways were investigated in conjunction with tandem mass spectrometry (MS/MS). The results showed that there were very different characteristic fragment ions in the pos. ion MS/MS spectra and the neg. ion MS/MS spectra.

IT **653566-23-5P 653566-24-6P 653566-25-7P 653566-26-8P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(preparation and mass spectral fragmentation of; characteristic fragmentation behavior of phosphoamino acid conjugates with 3'-azido-3'-deoxythymidine by ESI-MS)

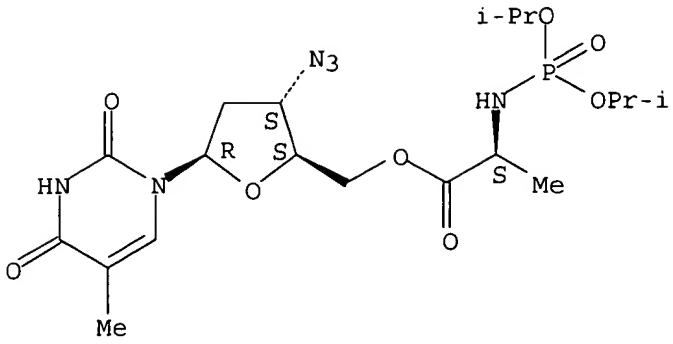
RN 653566-23-5 HCAPLUS
CN L-Phenylalanine, N-[bis(1-methylethoxy)phosphinyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



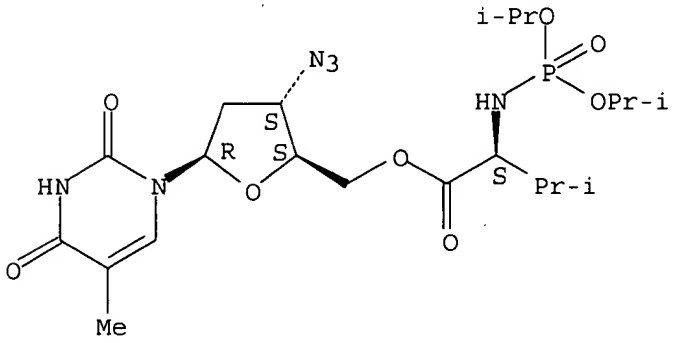
RN 653566-24-6 HCAPLUS
CN L-Alanine, N-[bis(1-methylethoxy)phosphinyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



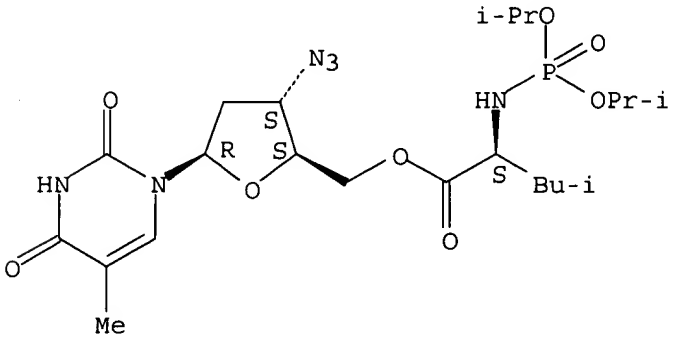
RN 653566-25-7 HCAPLUS
CN L-Valine, N-[bis(1-methylethoxy)phosphinyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 653566-26-8 HCAPLUS
CN L-Leucine, N-[bis(1-methylethoxy)phosphinyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:777522 HCAPLUS
DOCUMENT NUMBER: 139:296970
TITLE: Peptide conjugates for protecting and administering active agents
INVENTOR(S): Piccariello, Thomas; Kirk, Randal J.; Olon, Lawrence P.
PATENT ASSIGNEE(S): New River Parmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 436 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003079972	A2	20031002	WO 2003-US5524	20030224
WO 2003079972	A3	20040318		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004063628	A1	20040401	US 2002-156527	20020529
CA 2477088	AA	20031002	CA 2003-2477088	20030224
EP 1490090	A2	20041229	EP 2003-713634	20030224
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.:

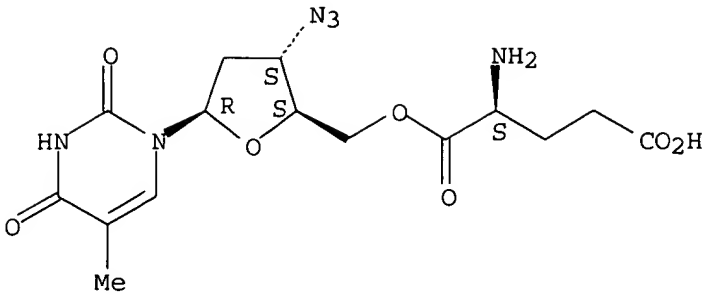
US 2002-358381P	P	20020222
US 2002-366258P	P	20020322
US 2002-156527	A	20020529
US 1999-265415	B2	19990310
US 1999-411238	B2	19991004
WO 2000-US5693	A	20000306
US 2000-642820	A2	20000822
US 2001-986426	A2	20011108
WO 2003-US5524	W	20030224

AB The present invention relates to active agent delivery systems and more specifically to compns. that comprise amino acids, as single amino acids or peptides, covalently attached to active agents and methods for administering conjugated active agent compns. E.g., poly(glutamic acid) was linked to a number of active agents such as cephalexin and atenolol. In vitro and in vivo performance studies were carried out such as caco-2 human intestinal epithelia cell studies which indicated the conjugates enhance oral delivery.

IT **607706-93-4P 607706-98-9P 607706-99-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(peptide conjugates for protecting and administering active agents)

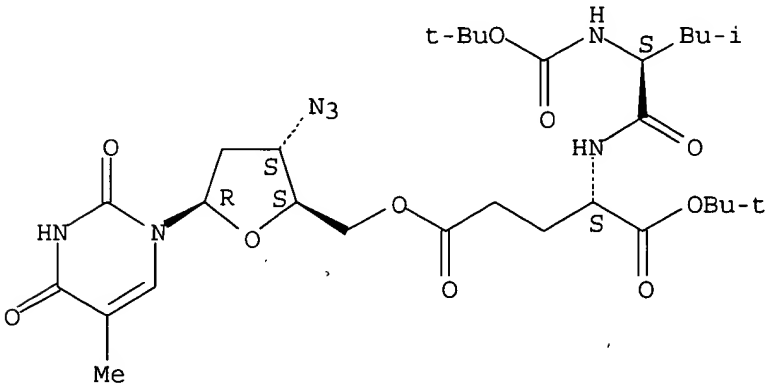
RN 607706-93-4 HCAPLUS
CN L-Glutamic acid, (1→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 607706-98-9 HCAPLUS
CN L-Glutamic acid, N-[(1,1-dimethylethoxy)carbonyl]-L-leucyl-, 21-(1,1-dimethylethyl) ester, (25→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

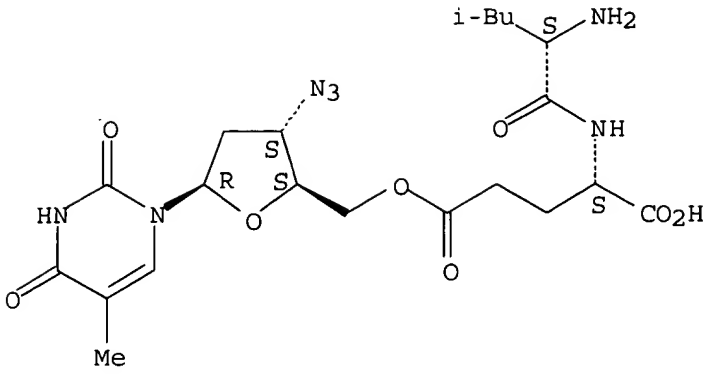


RN 607706-99-0 HCAPLUS
CN L-Glutamic acid, L-leucyl-, (25→5')-ester with 3'-azido-3'-deoxythymidine, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

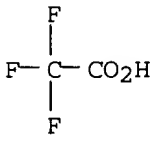
CRN 607706-97-8
CMF C21 H31 N7 O8

Absolute stereochemistry.



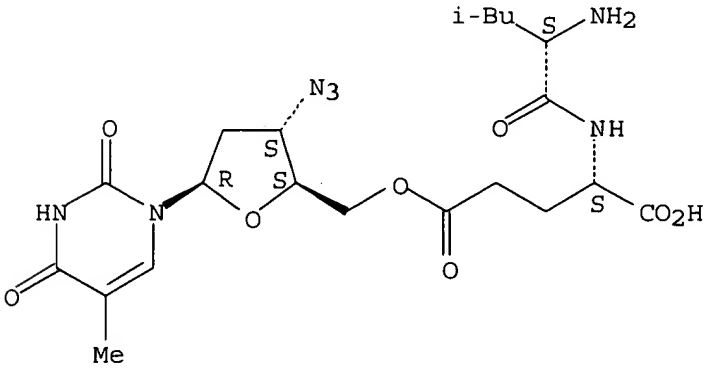
CM 2

CRN 76-05-1
CMF C2 H F3 O2



IT **607706-97-8P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(peptide conjugates for protecting and administering active agents)
RN 607706-97-8 HCAPLUS
CN L-Glutamic acid, L-leucyl-, (25→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 7 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:509434 HCAPLUS
DOCUMENT NUMBER: 140:52745

TITLE: "Double-drugs": a novel class of prodrug forms of HIV protease inhibitors conjugated with AZT by spontaneously cleavable linkers

AUTHOR(S): Kiso, Yoshiaki; Matsumoto, Hikaru; Hamawaki, Tomonori; Ota, Hisashi; Kimura, Tooru; Hayashi, Yoshio

CORPORATE SOURCE: Department of Medicinal Chemistry, Center for Frontier Research in Medicinal Science, Kyoto Pharmaceutical University, Kyoto, 607-8412, Japan

SOURCE: Peptides 2000, Proceedings of the European Peptide Symposium, 26th, Montpellier, France, Sept. 10-15, 2000 (2001), Meeting Date 2000, 153-154. Editor(s): Martinez, Jean; Fehrentz, Jean-Alain. Editions EDK: Paris, Fr.
CODEN: 69EDWK; ISBN: 2-84254-048-4

DOCUMENT TYPE: Conference

LANGUAGE: English

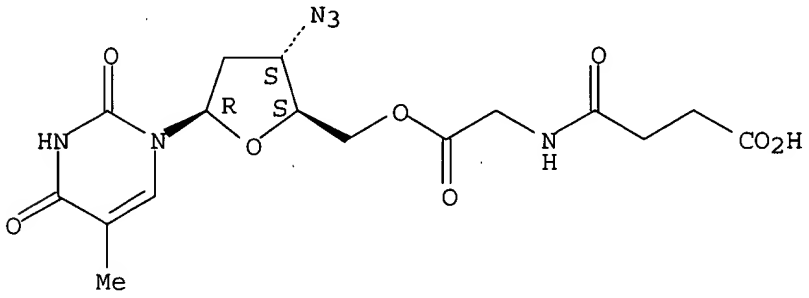
AB Novel hybrid-type prodrug anti-HIV agents were developed by conjugating HIV protease inhibitors with nucleoside reverse transcriptase inhibitor, 3'-azido-3'-deoxy-thymidine (AZT) using a series of linkers. Disintegration behavior of the prodrugs was determined as well as antiHIV activity.

IT **364764-34-1 364764-36-3**
RL: BSU (Biological study, unclassified); FMU (Formation, unclassified); BIOL (Biological study); FORM (Formation, nonpreparative)
(design and activity of double drug prodrug forms of HIV protease inhibitors conjugated with AZT by spontaneously cleavable linkers)

RN 364764-34-1 HCAPLUS

CN Thymidine, 3'-azido-3'-deoxy-, 5'-[[(3-carboxy-1-oxopropyl)amino]acetate] (9CI) (CA INDEX NAME)

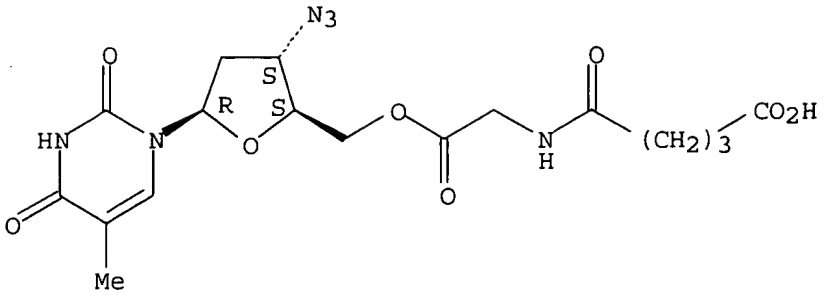
Absolute stereochemistry.



RN 364764-36-3 HCAPLUS

CN Thymidine, 3'-azido-3'-deoxy-, 5'-[[(4-carboxy-1-oxobutyl)amino]acetate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



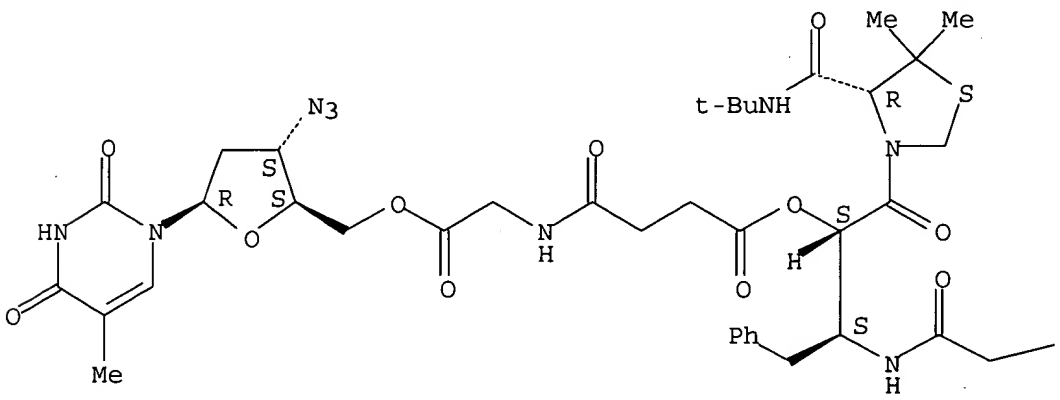
IT **288399-75-7P**, KNI 1038 **288399-76-8P**, KNI 1039
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(design and activity of double drug prodrug forms of HIV protease inhibitors conjugated with AZT by spontaneously cleavable linkers)

RN 288399-75-7 HCAPLUS

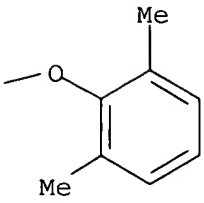
CN Glycine, N-[4-[(1S,2S)-1-[[(4R)-4-[[(1,1-dimethylethyl)amino]carbonyl]-5,5-dimethyl-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,4-dioxobutyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



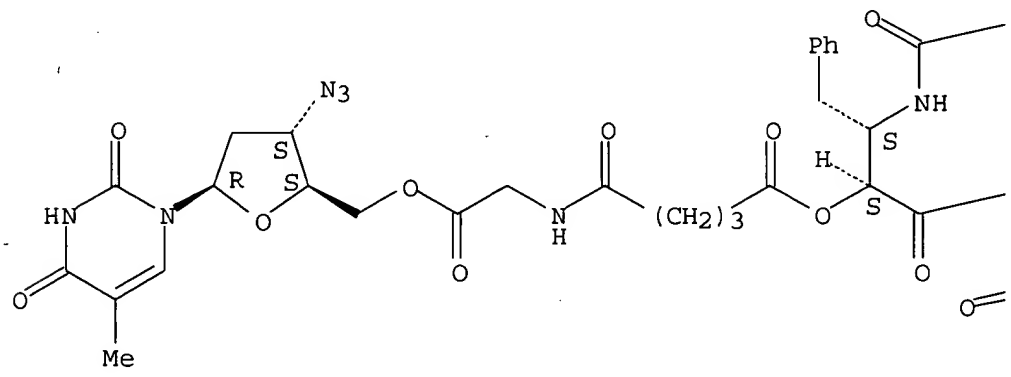
PAGE 1-B

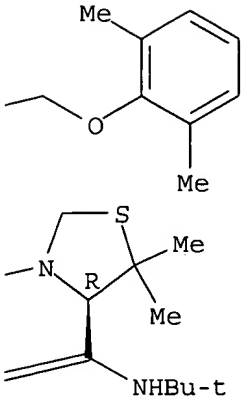


RN 288399-76-8 HCAPLUS
CN Glycine, N-[5-[(1S,2S)-1-[[(4R)-4-[[(1,1-dimethylethyl)amino]carbonyl]-5,5-dimethyl-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,5-dioxopentyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A





REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

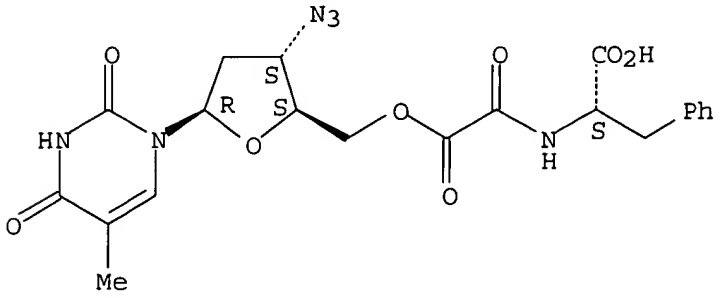
L12 ANSWER 8 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:786258 HCAPLUS
DOCUMENT NUMBER: 138:395382
TITLE: Antiretroviral activity and cytotoxicity of novel zidovudine (AZT) derivatives and the relation to their chemical structure
AUTHOR(S): Turk, Gabriela; Moroni, Guillermo; Pampuro, Sandra; Brinon, Margarita C.; Salomon, Horacio
CORPORATE SOURCE: School of Medicine, Department of Microbiology, National Reference Center for AIDS, University of Buenos Aires, Buenos Aires, C1121ABG, Argent.
SOURCE: International Journal of Antimicrobial Agents (2002), 20(4), 282-288
CODEN: IAAGEA; ISSN: 0924-8579
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Zidovudine (AZT) was the first nucleoside analog licensed for the treatment of HIV infection. Efforts have continuously been made to improve the therapeutic characteristics of this drug, most of them focussed on prodrugs design. Here we describe the anti-HIV-1 activity and cytotoxicity of six novel AZT derivs. namely 3'-azido-3'-deoxy-5'-O-oxalyl-N-valinethymidine, 3'-azido-3'-deoxy-5'-O-oxalyl-N-leucinethymidine, 3'-azido-3'-deoxy-5'-O-oxalyl-N-isoleucinethymidine, 3'-azido-3'-deoxy-5'-O-oxalyl-N-phenylalaninethymidine, 3'-azido-3'-deoxy-5'-O-oxalylthymidine acid, 3'-azido-3'-deoxy-5'-O-isonicotinoylthymidine and 5-chloro-6-hydroxy-5,6-dihydro-3'-azido-3'-deoxythymidine which were perfectly characterized. AZT-Val, AZT-Leu, AZT-iLeu, AZT-Phen, AZT-Ac and AZT-Iso have shown a similar or higher selectivity index than that of AZT itself, in one or both of the different cell cultures used (PBMC and MT2). However, AZT-ClOH showed no anti-HIV activity. These results suggest that using amino acids in the design of AZT derivs. improves AZT activity.

IT **395089-94-8 395089-95-9 395089-96-0 395089-97-1**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiretroviral structure activity of zidovudine derivs.)
RN 395089-94-8 HCAPLUS

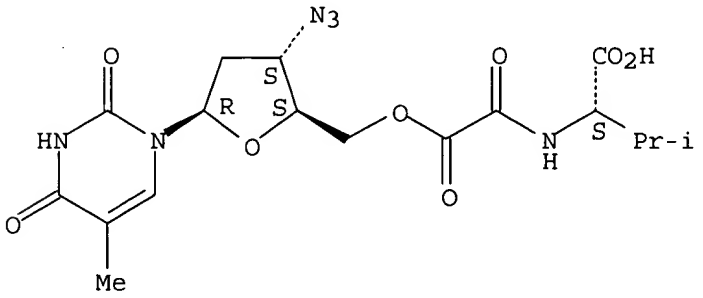
CN L-Phenylalanine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



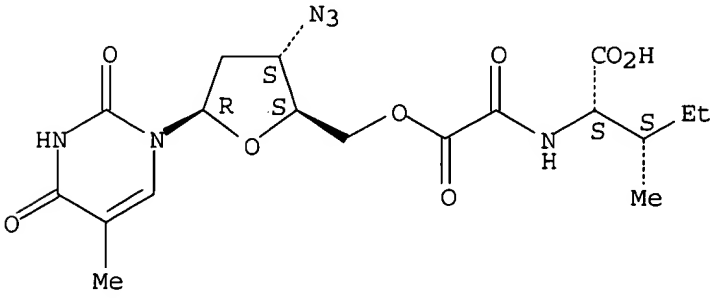
RN 395089-95-9 HCAPLUS
CN L-Valine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



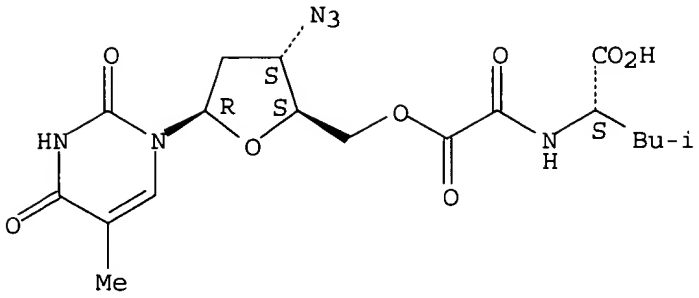
RN 395089-96-0 HCAPLUS
CN L-Isoleucine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 395089-97-1 HCAPLUS
CN L-Leucine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 9 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:692524 HCAPLUS
DOCUMENT NUMBER: 138:331224
TITLE: Prodrug forms of peptidomimetic HIV protease inhibitors using intramolecular cyclization reaction
AUTHOR(S): Kiso, Yoshiaki; Matsumoto, Hikaru; Hamawaki, Tomonori; Sohma, Youbei; Kimura, Tooru; Hayashi, Yoshio
CORPORATE SOURCE: Department of Medicinal Chemistry, Center for Frontier Research in Medicinal Science, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto, 607-8412, Japan
SOURCE: Peptides: The Wave of the Future, Proceedings of the Second International and the Seventeenth American Peptide Symposium, San Diego, CA, United States, June 9-14, 2001 (2001), 650-651. Editor(s): Lebl, Michal; Houghten, Richard A. American Peptide Society: San Diego, Calif.
CODEN: 69DBAL; ISBN: 0-9715560-0-8
DOCUMENT TYPE: Conference
LANGUAGE: English

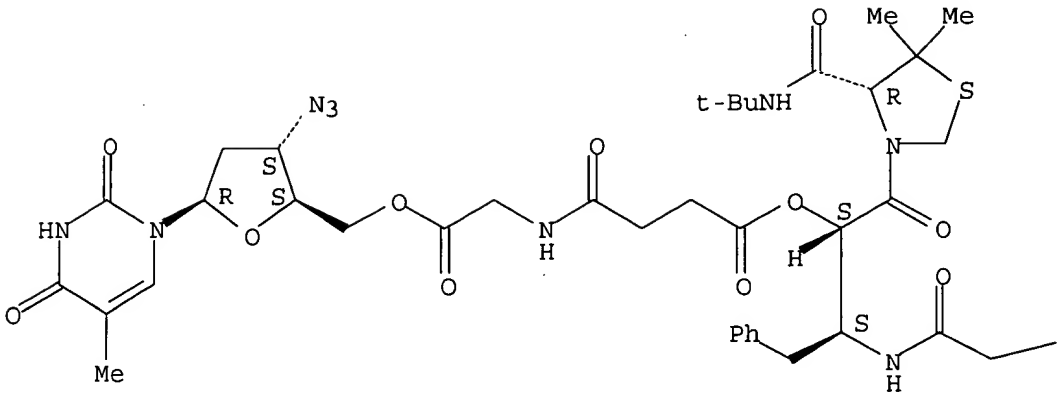
AB Small dipeptide-based HIV-1 protease inhibitors containing the hydroxymethylcarbonyl isostere were examined The prodrug forms of a peptidomimetic HIV protease inhibitor, KNI-727, conjugated with a nucleoside reverse transcriptase inhibitor, AZT, were designed and synthesized to enhance the anti-HIV activity and improve the physicochem. characteristics. Conjugates using a succinyl amino acid linker were shown to cause the faster release of the parent components via the spontaneous imide formation compared to conjugates using a glutaryl amino acid linker, as expected from the energetically favorable cyclization to the five-membered ring. Prodrugs with an ionized amino group at the solubilizing moiety showed a remarkable increase of water-solubility compared to the parent drug.

IT **288399-75-7**, KNI-1038 **288399-76-8**, KNI-1039
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prodrug forms of peptidomimetic HIV proteinase inhibitors using intramol. cyclization reaction)

RN 288399-75-7 HCAPLUS
CN Glycine, N-[4-[(1S,2S)-1-[[(4R)-4-[[(1,1-dimethylethyl)amino]carbonyl]-5,5-dimethyl-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,4-dioxobutyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



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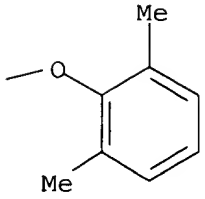
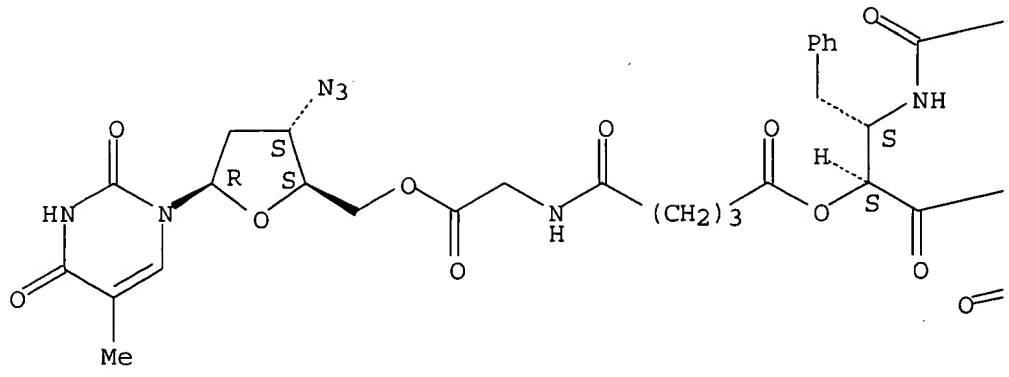


RN 288399-76-8 HCAPLUS
CN Glycine, N-[5-[(1S,2S)-1-[[(4R)-4-[[(1,1-dimethylethyl)amino]carbonyl]-5,5-dimethyl-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,5-dioxopentyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



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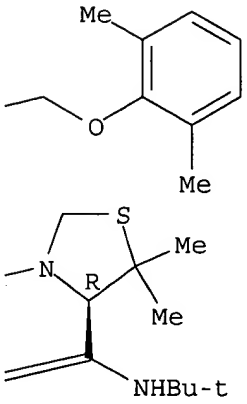

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 10 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:556104 HCAPLUS
DOCUMENT NUMBER: 137:109489
TITLE: Compositions comprising a polypeptide and an active agent
INVENTOR(S): Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randal J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 34 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 2002099013	A1	20020725	US 2001-933708		20010822
US 2004087483	A1	20040506	US 2002-136433		20020502
PRIORITY APPLN. INFO.:			US 2000-247556P	P	20001114
			US 2000-247558P	P	20001114
			US 2000-247559P	P	20001114
			US 2000-247560P	P	20001114
			US 2000-247561P	P	20001114
			US 2000-247594P	P	20001114
			US 2000-247595P	P	20001114
			US 2000-247606P	P	20001114
			US 2000-247607P	P	20001114
			US 2000-247608P	P	20001114
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			US 2000-247612P	P	20001114
			US 2000-247620P	P	20001114
			US 2000-247621P	P	20001114
			US 2000-247634P	P	20001114
			US 2000-247635P	P	20001114
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			US 2000-247799P	P	20001114
			US 2000-247800P	P	20001114
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			US 2000-247807P	P	20001114
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			US 2000-247833P	P	20001114
			US 2000-247926P	P	20001114
			US 2000-247927P	P	20001114
			US 2000-247928P	P	20001114
			US 2000-247929P	P	20001114
			US 2000-247930P	P	20001114
			US 2000-642820	A2	20000822
			US 2000-248607P	P	20001116
			US 2001-933708	A2	20010822

AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an active agent to a patient by administering the composition to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepared from Glu(OBut)NCA and cephalexin hydrochloride.

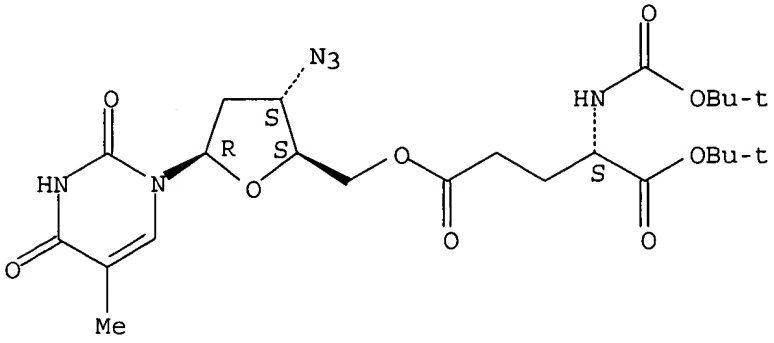
IT **125780-85-0P 125780-86-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(compns. comprising a polypeptide and an active agent)

RN 125780-85-0 HCAPLUS

CN L-Glutamic acid, N-[(1,1-dimethylethoxy)carbonyl]-, 1-(1,1-dimethylethyl)

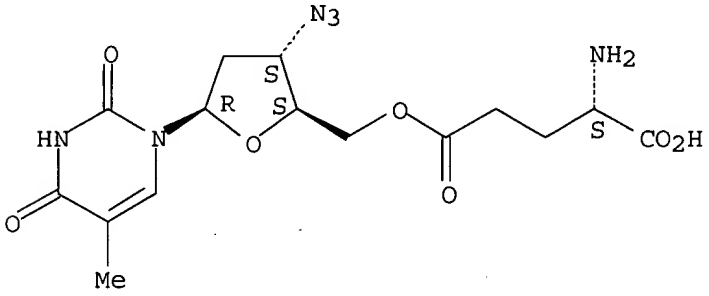
ester, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 125780-86-1 HCAPLUS
CN L-Glutamic acid, 5→5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



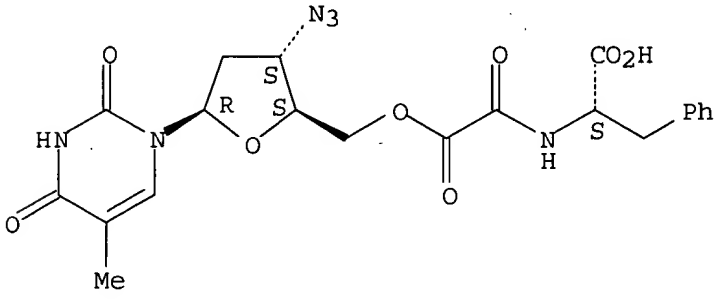
L12 ANSWER 11 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:505577 HCAPLUS
DOCUMENT NUMBER: 138:247911
TITLE: Lipophilic character of novel amino acid derivatives of zidovudine with anti-HIV activity
AUTHOR(S): Moroni, Guillermo N.; Quevedo, Mario A.; Ravetti, Soledad; Brinon, Margarita C.
CORPORATE SOURCE: Departamento de Farmacia, Facultad de Ciencias Quimicas, Universidad Nacional de Cordoba, Cordoba, 5000, Argent.
SOURCE: Journal of Liquid Chromatography & Related Technologies (2002), 25(9), 1345-1365
CODEN: JLCTFC; ISSN: 1082-6076
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:247911
AB The lipophilic properties of a novel series of zidovudine amino acid derivs. were measured using chromatog. techniques, reversed-phase thin-layer chromatog. (RP-TLC) and reversed-phase high-performance liquid chromatog. (RP-HPLC), as well as the classic shake flask (log Po/w) and theor. CLOGP methods. These novel derivs., obtained by association of

zidovudine (AZT) with the essential amino acids leucine (AZT-Leu), isoleucine (AZT-iLeu), phenylalanine (AZT-Phe), valine (AZT-Val), proline (AZT-Prol) and tryptophane (AZT-Tryp), exhibited an increased log Po/w as compared with the parent compound as follows: AZT-iLeu > AZT-Leu > AZT-Tryp > AZT-Val > AZT-Phe > AZT-Prol > AZT > Thym. All assays were performed using a buffer, pH2, as mobile phase, at which the mentioned compds. were completely as their non-ionized forms. In addition, good linear relationships were observed between log P values determined by the shake flask method (log Po/w), and those obtained by chromatog. techniques (log PRP-TLC and log PRP-HPLC) and from theor. calcns. using the CLOGP program (log PCLOGP). These results demonstrate the applicability of the chromatog. methods to describe the lipophilic properties of this family of compds.

IT **395089-94-8P 395089-95-9P 395089-96-0P 395089-97-1P 502545-74-6P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and lipophilic properties measured by chromatog. methods of amino acid derivs. of zidovudine with anti-HIV activity)

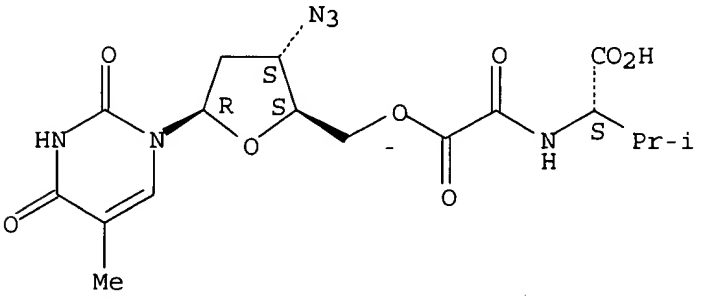
RN 395089-94-8 HCAPLUS
CN L-Phenylalanine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



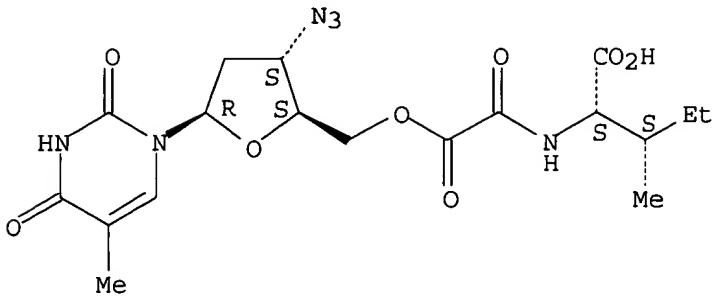
RN 395089-95-9 HCAPLUS
CN L-Valine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



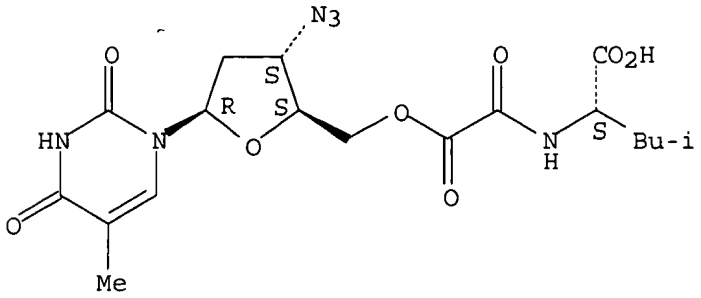
RN 395089-96-0 HCAPLUS
CN L-Isoleucine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



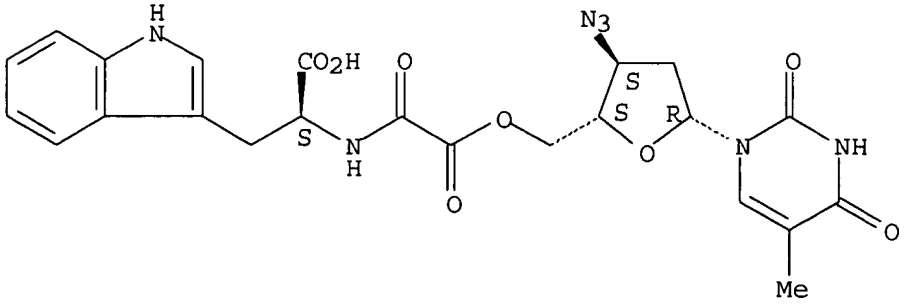
RN 395089-97-1 HCAPLUS
CN L-Leucine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 502545-74-6 HCAPLUS
CN L-Tryptophan, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 12 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:332011 HCAPLUS
DOCUMENT NUMBER: 136:355482
TITLE: Compositions comprising a polypeptide and an active agent

INVENTOR(S): Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randall J.
PATENT ASSIGNEE(S): New River Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002034237	A1	20020502	WO 2001-US26142	20010822
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
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US 2004127397	A1	20040701	US 2003-727565	20031205

PRIORITY APPLN. INFO.:

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US 2000-247621P	P	20001114
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US 2000-247698P	P	20001114
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US 2000-247802P	P	20001114
US 2000-247803P	P	20001114
US 2000-247804P	P	20001114
WO 2001-US26142	W	20010822

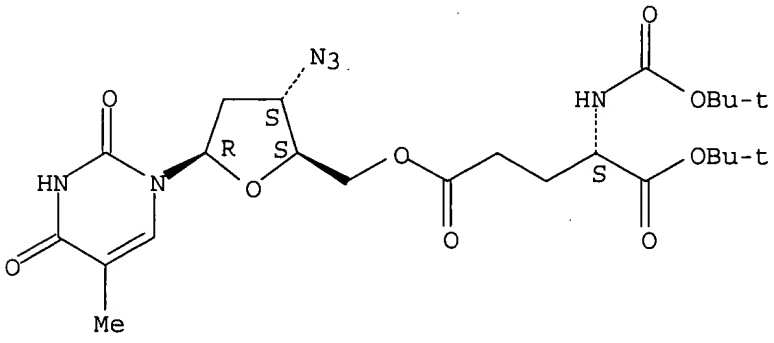
AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an active agent to a patient by administering the composition to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepared from Glu(OBut)NCA and cephalexin hydrochloride.

IT **125780-85-0P 125780-86-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(compns. comprising a polypeptide and an active agent)

RN 125780-85-0 HCAPLUS

CN L-Glutamic acid, N-[(1,1-dimethylethoxy)carbonyl]-, 1-(1,1-dimethylethyl) ester, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

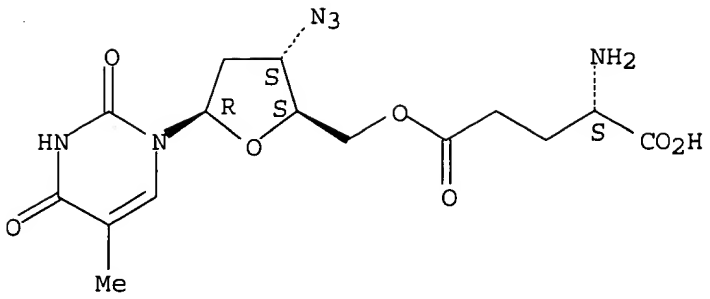
Absolute stereochemistry.



RN 125780-86-1 HCAPLUS

CN L-Glutamic acid, 5→5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

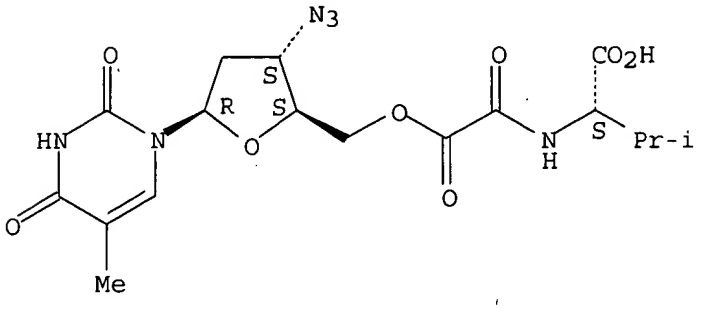
L12 ANSWER 13 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:323220 HCAPLUS
DOCUMENT NUMBER: 137:140719
TITLE: Synthesis and in vitro antibacterial activity of novel 5'-O-analog derivatives of Zidovudine as potential prodrugs
AUTHOR(S): Moroni, Guillermo N.; Bogdanov, Patricia M.; Brinon, Margarita C.
CORPORATE SOURCE: Departamento de Farmacia, Facultad de Ciencias Quimicas, Universidad Nacional de Cordoba, Cordoba, 5000, Argent.
SOURCE: Nucleosides, Nucleotides & Nucleic Acids (2002), 21(3), 231-241
CODEN: NNNAFY; ISSN: 1525-7770
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:140719

AB An efficient, short synthesis of four potential prodrugs of 3'-azido-3'-deoxythymidine (AZT) and their antibacterial activity are reported. The 5'-OH group of AZT was functionalized with oxalyl chloride obtaining an acyl chloride derivative (AZT-Ox), which by further transformation with leucine, isoleucine and valine amino acids led to the corresponding AZT analogs, namely AZT-Leu, AZT-iLeu and AZT-Val. A carboxyl acid derivative (AZT-Ac) was also obtained by hydrolysis of AZT-Ox. These compds., which exhibit anti HIV activity, have killed collection and clin. strains of some opportunistic infectious agents in AIDS-related complex. Thus, the clin. strains, K. oxytoca, S. typhi and K. pneumoniae, and collection strain K. pneumoniae ATCC 10031 showed sensitivity to antibiotics. The activity order for the studied compds. against the most sensitive strain (K. pneumoniae ATCC 10031) was AZT-Leu > AZT-iLeu > AZT-Val > AZT-Ac > AZT. On the other hand, the activity order for the second most sensitive strain (K. oxytoca) was AZT-Leu > AZT-Val = AZT-Ac > AZT-iLeu > AZT. The most effective antibacterial drug AZT-Leu, (M.I.C. = 0.125 μg mL-1) was sixteen times more active than AZT (AZT, M.I.C. = 2 μg mL-1) against K. pneumoniae ATCC 10031. Thus, this compound may therefore have better clin. potential than AZT for the treatment of AIDS-related complex.

IT **395089-95-9P 395089-96-0P 395089-97-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis, in vitro antibacterial, and anti-HIV activities of novel 5'-O-(amino acid) derivs. of Zidovudine)

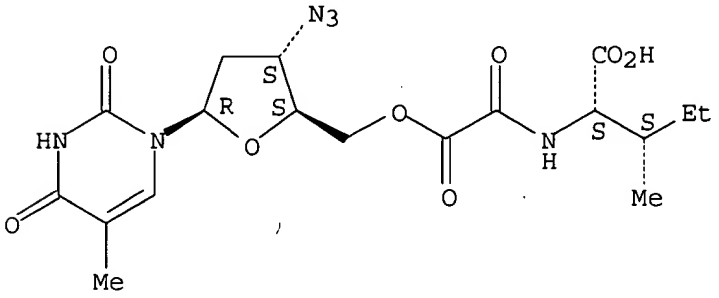
RN 395089-95-9 HCAPLUS
CN L-Valine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



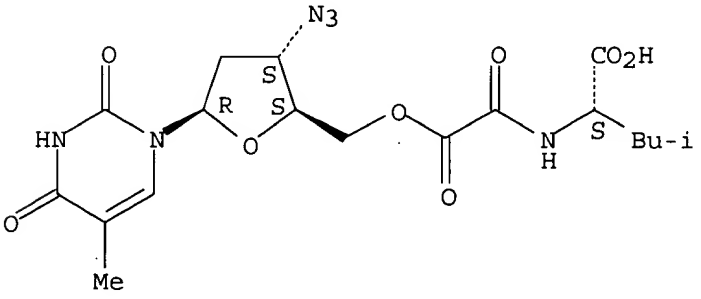
RN 395089-96-0 HCAPLUS
CN L-Isoleucine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 395089-97-1 HCAPLUS
CN L-Leucine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 14 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:795165 HCAPLUS

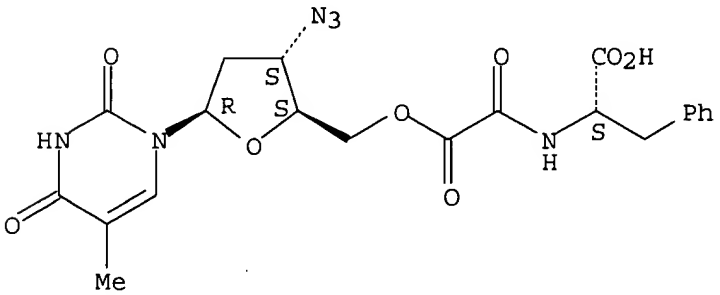
DOCUMENT NUMBER: 136:144610
TITLE: Human Serum Albumin Binding of Novel Antiretroviral Nucleoside Derivatives of AZT
AUTHOR(S): Quevedo, Mario A.; Moroni, Guillermo N.; Brinon, Margarita C.
CORPORATE SOURCE: Departamento de Farmacia, Facultad de Ciencias Quimicas, Universidad Nacional de Cordoba, Cordoba, 5000, Argent.
SOURCE: Biochemical and Biophysical Research Communications (2001), 288(4), 954-960
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The binding of novel nucleoside derivs. (2-7) to the Human Serum Albumin (HSA) was studied using zidovudine (AZT), as standard compound The applicability of two different techniques to sep. unbound drug from drug-protein complex was analyzed: the gel filtration and ultrafiltration methods. Ultrafiltration was found to be an adequate procedure for the separation of unbounded drug from the drug-protein complex. Incubation temperature ranging from 0 to 37° did not modify considerably the bound fractions. The same effects were observed as HSA concentration was modified. Binding assays of studied compds. to purified 1% (w/v) HSA at 0°, indicate that bound fraction of 2-7 ranges from 13 to 47%, exhibiting a higher affinity to HSA than AZT (12%), which would introduce some interesting improvements in their pharmacokinetic properties. In addition, by means of displacement studies using HSA site specific drugs such as diazepam and salicylate, it was determined that AZT binds to site I of the HSA mol., by a mainly entropy driven process (ΔS = 10.834 cal/mol °K), being these observations extensive to 2-7. Some structural basis to explain enhanced affinity of these novel derivs. was also established. (c) 2001 Academic Press.

IT **395089-94-8 395089-95-9 395089-96-0 395089-97-1**
RL: PKT (Pharmacokinetics); PRP (Properties); BIOL (Biological study) (human serum albumin binding of novel antiretroviral nucleoside derivs. of AZT)

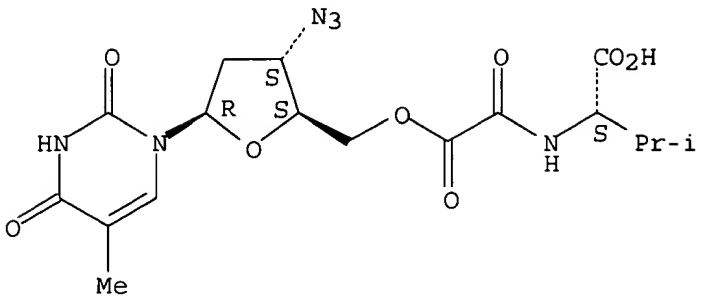
RN 395089-94-8 HCAPLUS
CN L-Phenylalanine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



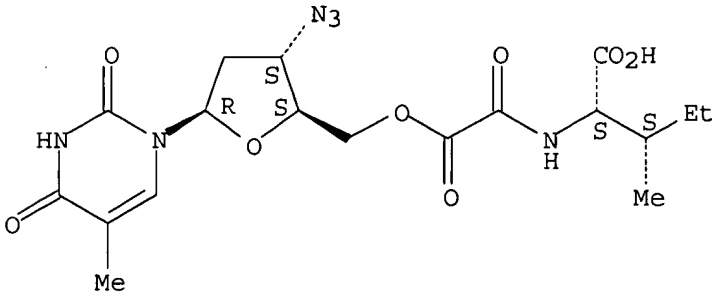
RN 395089-95-9 HCAPLUS
CN L-Valine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



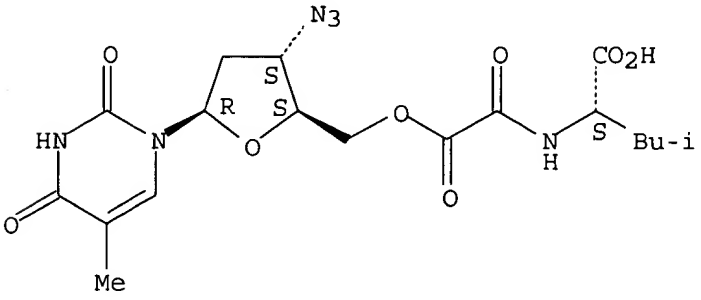
RN 395089-96-0 HCAPLUS
CN L-Isoleucine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 395089-97-1 HCAPLUS
CN L-Leucine, N-(carboxycarbonyl)-, (N→5')-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 15 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:426034 HCAPLUS
DOCUMENT NUMBER: 135:288998
TITLE: Design, synthesis, and biological evaluation of anti-HIV double-drugs conjugates of HIV protease

inhibitors with a reverse transcriptase inhibitor through spontaneously cleavable linkers

AUTHOR(S): Matsumoto, H.; Kimura, T.; Hamawaki, T.; Kumagai, A.; Goto, T.; Sano, K.; Hayashi, Y.; Kiso, Y.

CORPORATE SOURCE: Center for Frontier Research in Medicinal Science, Department of Medicinal Chemistry, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto, 607-8412, Japan

SOURCE: Bioorganic & Medicinal Chemistry (2001), 9(6), 1589-1600
CODEN: BMECEP; ISSN: 0968-0896

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 135:288998

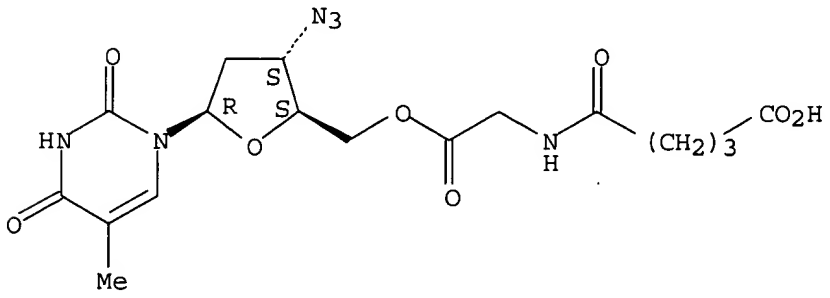
AB Based on the prodrug concept as well as the combination of two different classes of anti-HIV agents, we designed and synthesized a series of anti-HIV double-drugs consisting of HIV protease inhibitors conjugated with a nucleoside reverse transcriptase inhibitor in an effort to enhance the antiviral activity. For the conjugation, a series of linkers that conjoins the two different classes of inhibitors has been investigated. Double-drugs using a succinyl amino acid linker were shown to release the parent drugs via spontaneous imide formation at a faster rate compared to compds. using a glutaryl amino acid linker, as expected from the energetically favorable cyclization to the five-membered ring. Among the double-drugs, KNI-1039 (I) with a glutarylglycine linker exhibited extremely potent anti-HIV activity compared with that of the individual components. Double-drug I was relatively stable in culture medium, whereas it regenerated active species in cell homogenate. These results suggested that the synergistic enhancement of anti-HIV activities of I may be due to their ability to penetrate into the target cell and subsequent regeneration of two different classes of anti-HIV agents in the cytoplasm. KNI-1039, a double-drug conjugating an HIV protease inhibitor with AZT by a glutarylglycine linker, exhibited excellent anti-HIV activity.

IT **364764-36-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(design, synthesis, and biol. evaluation of anti-HIV double-drugs azidodeoxy nucleosides of HIV protease inhibitors with a reverse transcriptase inhibitor through spontaneously cleavable linkers)

RN 364764-36-3 HCAPLUS

CN Thymidine, 3'-azido-3'-deoxy-, 5'-[[(4-carboxy-1-oxobutyl)amino]acetate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



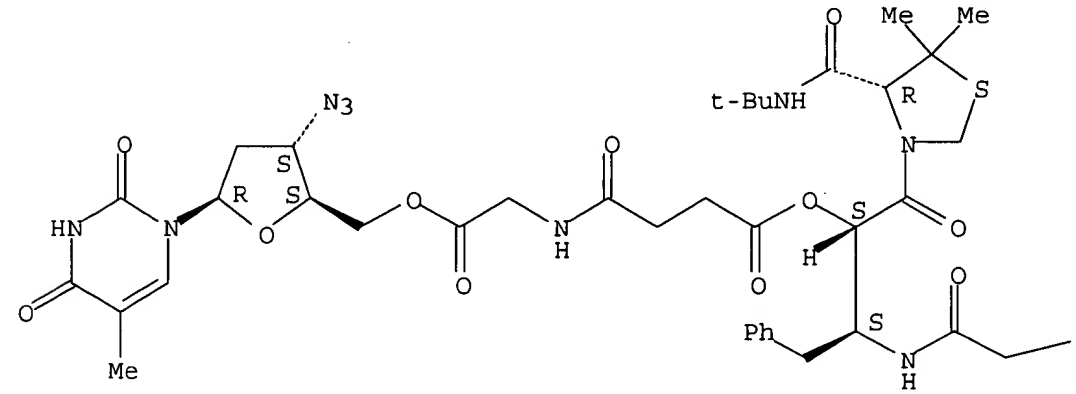
IT **288399-75-7P 288399-76-8P 362587-77-7P**
362587-78-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(design, synthesis, and biol. evaluation of anti-HIV double-drugs azidodeoxy nucleosides of HIV protease inhibitors with a reverse transcriptase inhibitor through spontaneously cleavable linkers)

RN 288399-75-7 HCAPLUS

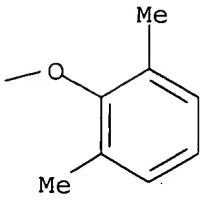
CN Glycine, N-[4-[(1S,2S)-1-[[(4R)-4-[[(1,1-dimethylethyl)amino]carbonyl]-5,5-dimethyl-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,4-dioxobutyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



PAGE 1-B



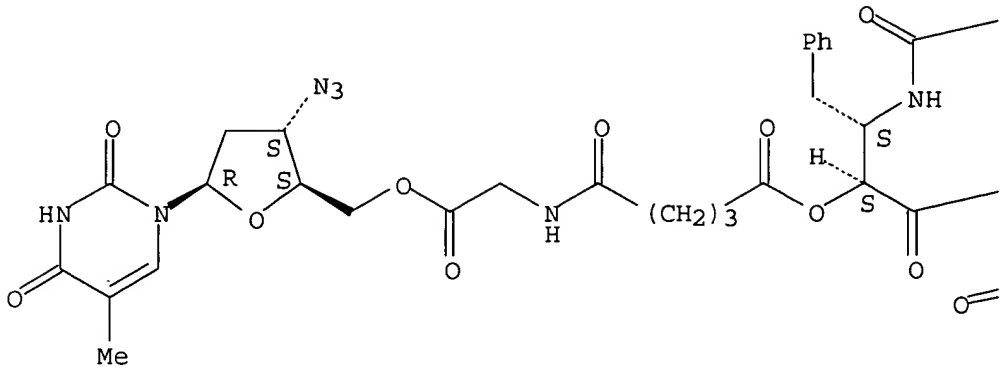
RN 288399-76-8 HCAPLUS

CN Glycine, N-[5-[(1S,2S)-1-[[(4R)-4-[[(1,1-dimethylethyl)amino]carbonyl]-5,5-dimethyl-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,5-dioxopentyl]-, 5'-ester with 3'-azido-3'-

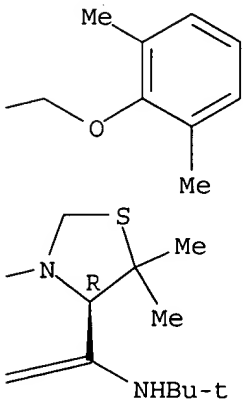
deoxythimidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



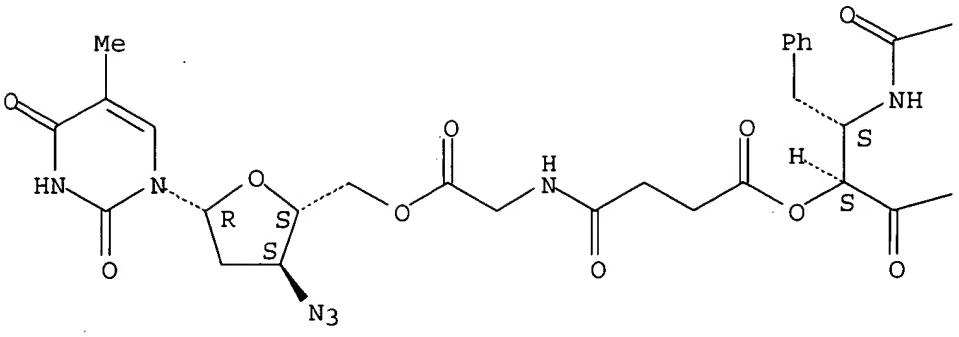
PAGE 1-B



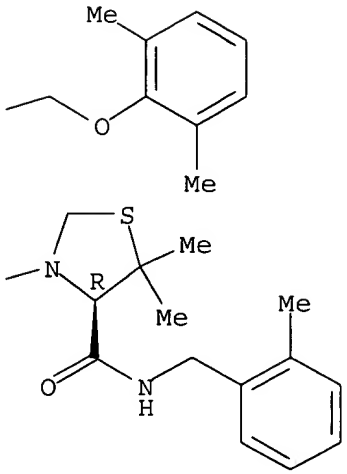
RN 362587-77-7 HCAPLUS
CN Glycine, N-[4-[(1S,2S)-1-[[(4R)-5,5-dimethyl-4-[[[(2-methylphenyl)methyl]amino]carbonyl]-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,4-dioxobutyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



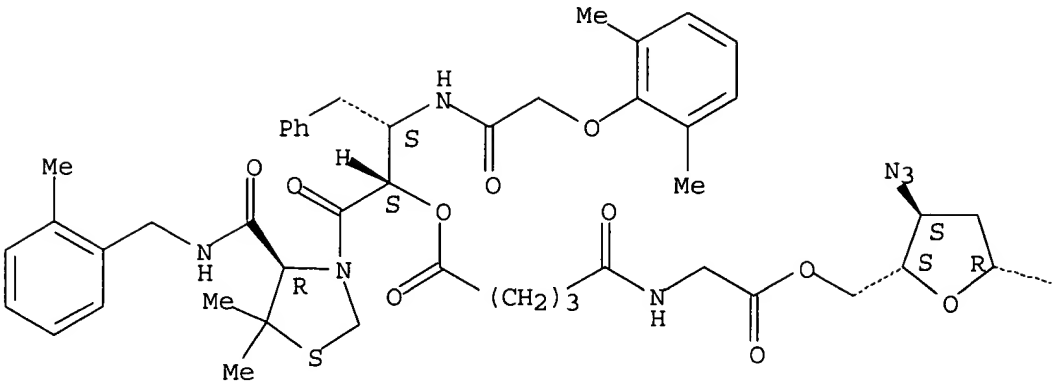
PAGE 1-B



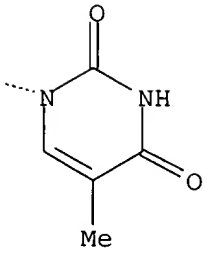
RN 362587-78-8 HCAPLUS
CN Glycine, N-[5-[(1S,2S)-1-[[(4R)-5,5-dimethyl-4-[[[(2-methylphenyl)methyl]amino]carbonyl]-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,5-dioxopentyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

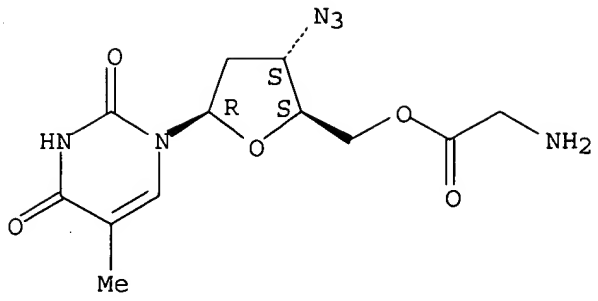


PAGE 1-B



IT **305322-74-1P 364764-34-1P 364764-37-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(design, synthesis, and biol. evaluation of anti-HIV double-drugs azidodeoxy nucleosides of HIV protease inhibitors with a reverse transcriptase inhibitor through spontaneously cleavable linkers)
RN 305322-74-1 HCAPLUS
CN Glycine, 5'-ester with 3'-azido-3'-deoxythymidine, monohydrochloride (9CI) (CA INDEX NAME)

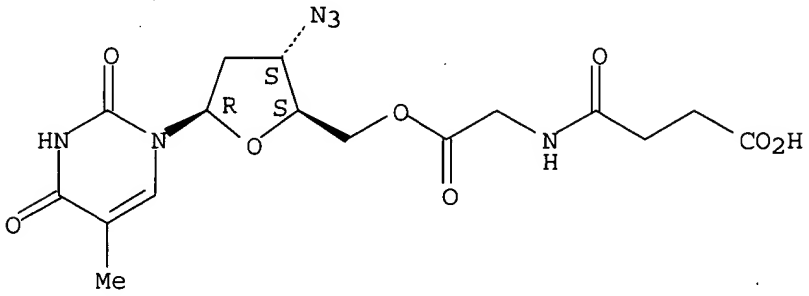
Absolute stereochemistry.



● HCl

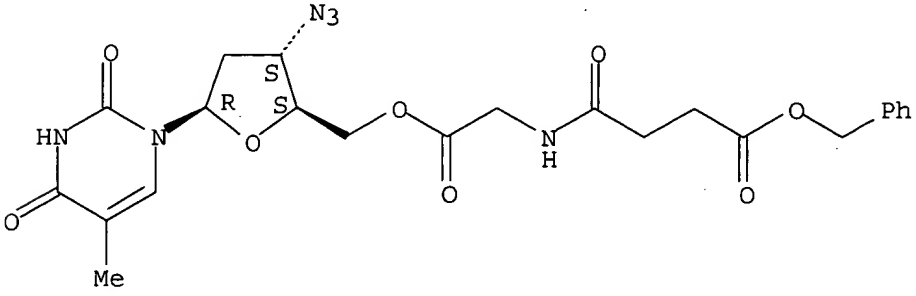
RN 364764-34-1 HCAPLUS
CN Thymidine, 3'-azido-3'-deoxy-, 5'-[[(3-carboxy-1-oxopropyl)amino]acetate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 364764-37-4 HCAPLUS
CN Thymidine, 3'-azido-3'-deoxy-, 5'-[[[1,4-dioxo-4-(phenylmethoxy)butyl]amino]acetate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 16 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:311772 HCAPLUS
DOCUMENT NUMBER: 135:266656

TITLE: Design of double-drug-type anti-HIV agents
AUTHOR(S): Kiso, Yoshiaki; Matsumoto, Hikaru; Hamawaki, Tomonori; Ota, Hisashi; Kimura, Tooru; Goto, Toshiyuki; Sano, Kouichi; Hayashi, Yoshio
CORPORATE SOURCE: Department of Medicinal Chemistry, Kyoto Pharmaceutical University, Kyoto, 607-8412, Japan
SOURCE: Peptide Science (2001), Volume Date 2000, 37th, 213-216
CODEN: PSCIFQ; ISSN: 1344-7661
PUBLISHER: Japanese Peptide Society
DOCUMENT TYPE: Journal
LANGUAGE: English

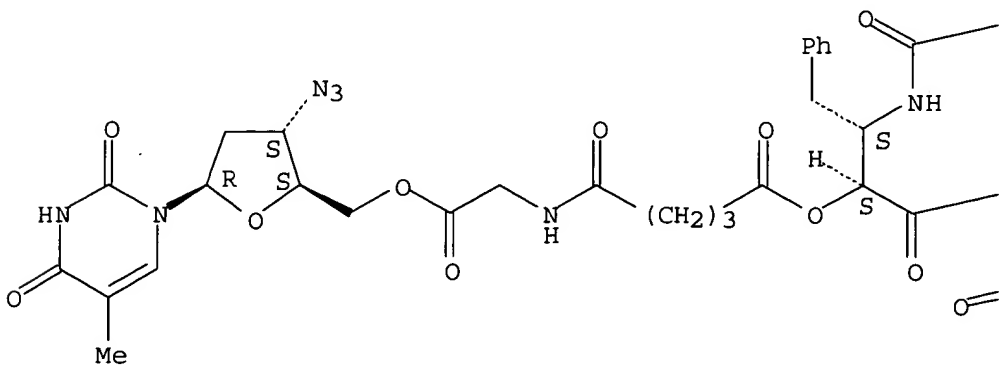
AB Based on the "double-drug" strategy, we had developed a potent prodrug-type anti-HIV agent, KNI-684, in which the carboxyl group of HIV PR inhibitors, KNI-413 was directly esterified with the 5'-hydroxyl group of a nucleoside RT inhibitor, 3'-azido-3'-deoxythimidine (AZT). The anti-HIV activity of KNI-684 was found to be more potent than that of AZT and the parent PR inhibitor. This result suggested the following: (a) The "double-drug" strategy involving the combination of two different classes of inhibitors together would enhance the anti-HIV efficacy synergistically, and (b) also be effective in the improvement of its physicochem. characteristics. In addition, for the conjugation, a series of linkers that conjoin the two different classes of inhibitors have been investigated. Among them, the hybrid-type prodrug (KNI-1039) of KNI-727 conjugated with AZT by a glutarylglycine linker exhibited extremely potent anti-HIV activity compared with that of the individual components.

IT **288399-76-8**, KNI-1039 **362587-77-7 362587-78-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(design of double-drug-type anti-HIV agents)

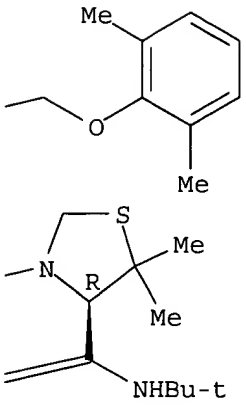
RN 288399-76-8 HCAPLUS
CN Glycine, N-[5-[(1S,2S)-1-[[(4R)-4-[[(1,1-dimethylethyl)amino]carbonyl]-5,5-dimethyl-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,5-dioxopentyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



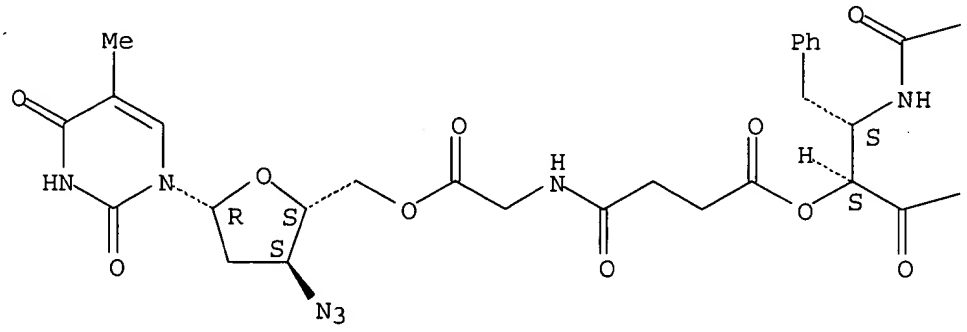
PAGE 1-B



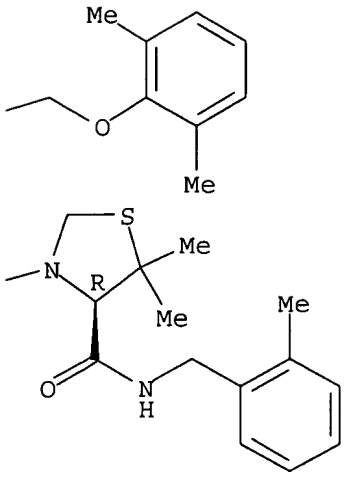
RN 362587-77-7 HCAPLUS
CN Glycine, N-[4-[(1S,2S)-1-[[(4R)-5,5-dimethyl-4-[[[(2-methylphenyl)methyl]amino]carbonyl]-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,4-dioxobutyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



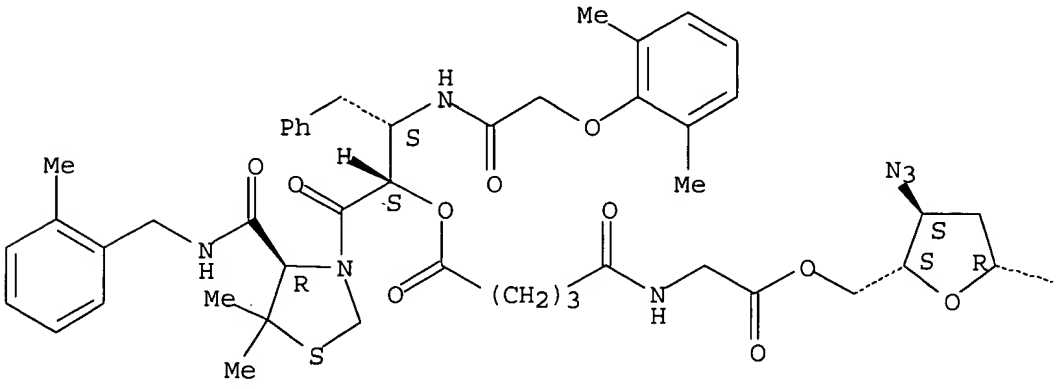
PAGE 1-B

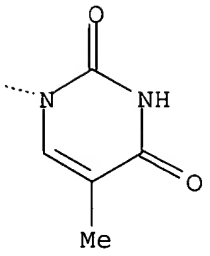


RN 362587-78-8 HCAPLUS
CN Glycine, N-[5-[(1S,2S)-1-[[(4R)-5,5-dimethyl-4-[[[(2-methylphenyl)methyl]amino]carbonyl]-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,5-dioxopentyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A





REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 17 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:780909 HCAPLUS
DOCUMENT NUMBER: 133:350514
TITLE: Preparation of multidrug-bonded compounds as anti-HIV agents
INVENTOR(S): Kiso, Yoshiaki; Fujino, Masahiko
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 16 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000309598	A2	20001107	JP 2000-54387	20000225
US 6440946	B1	20020827	US 1999-370543	19990809
CA 2281133	AA	20000825	CA 1999-2281133	19990830
PRIORITY APPLN. INFO.:			JP 1999-47557 A	19990225
OTHER SOURCE(S):	MARPAT 133:350514			

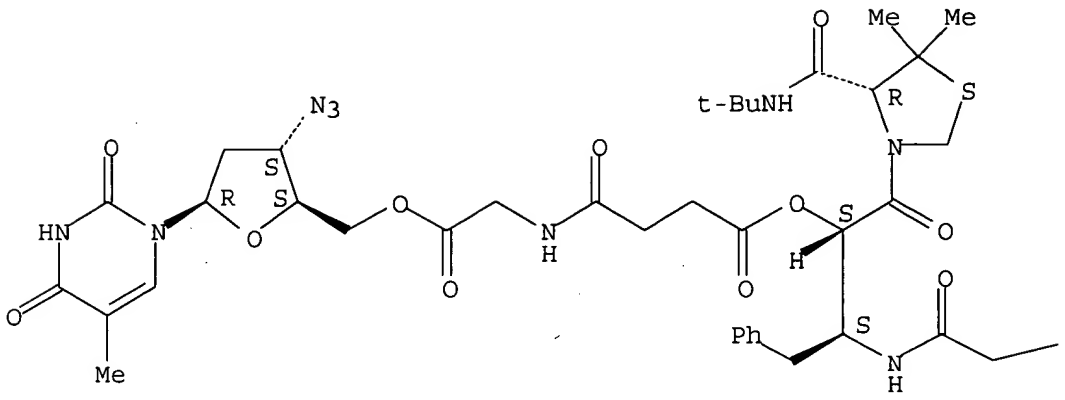
AB Prepared are compds. having a moiety of an anti-HIV agent having no affinity with cell surface protein, and another moiety of the same or different anti-HIV agent. Condensation of 266 mg KNI 852 with 50 mg AZT in the presence of DCC and 4-(dimethylamino)pyridine gave 163 mg of the corresponding ester, which showed anti-HIV activity with EC50 of 0.24 nM in HIV-1 IIIB-infected CEM-SS cell.

IT **288399-75-7P 288399-76-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of multidrug-bonded compds. as anti-HIV agents)
RN 288399-75-7 HCAPLUS
CN Glycine, N-[4-[(1S,2S)-1-[[(4R)-4-[[(1,1-dimethylethyl)amino]carbonyl]-5,5-dimethyl-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,4-dioxobutyl]-, 5'-ester with 3'-azido-3'-

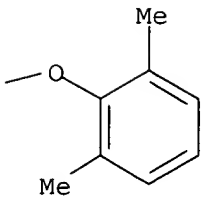
deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



PAGE 1-B

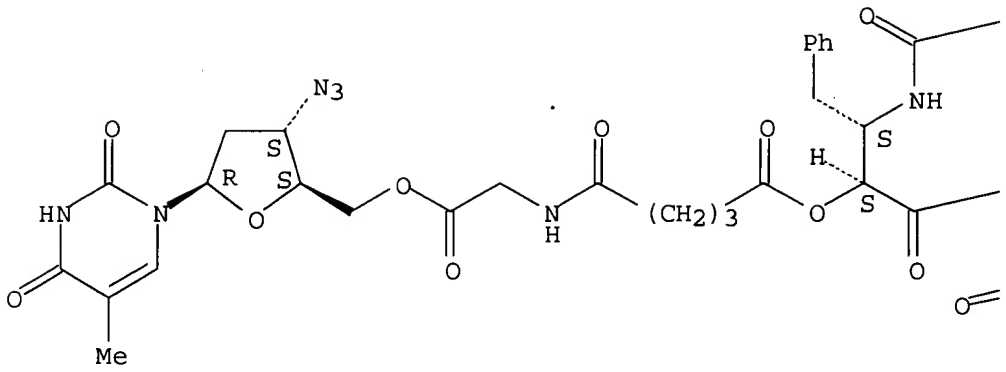


RN 288399-76-8 HCAPLUS

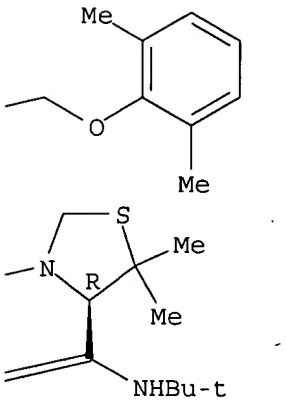
CN Glycine, N-[5-[(1S,2S)-1-[[(4R)-4-[[(1,1-dimethylethyl)amino]carbonyl]-5,5-dimethyl-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,5-dioxopentyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

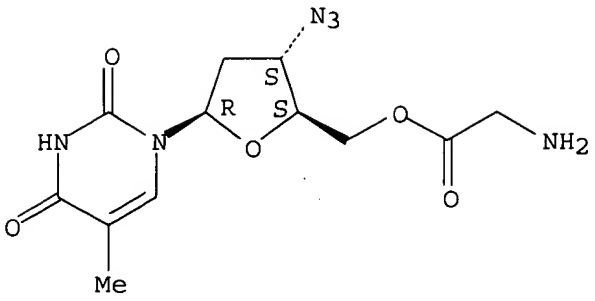


PAGE 1-B



IT **305322-74-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of multidrug-bonded compds. as anti-HIV agents)
RN 305322-74-1 HCAPLUS
CN Glycine, 5'-ester with 3'-azido-3'-deoxythymidine, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L12 ANSWER 18 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:419961 HCAPLUS
DOCUMENT NUMBER: 133:187619
TITLE: "Double-drugs"- a new class of prodrug form of an HIV protease inhibitor conjugated with a reverse transcriptase inhibitor by a spontaneously cleavable linker
AUTHOR(S): Matsumoto, Hikaru; Hamawaki, Tomonori; Ota, Hisashi; Kimura, Tooru; Goto, Toshiyuki; Sano, Kouichi; Hayashi, Yoshio; Kiso, Yoshiaki
CORPORATE SOURCE: Department of Medicinal Chemistry, Center for Frontier Research in Medicinal Science, Kyoto Pharmaceutical University, Kyoto, 607-8412, Japan
SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(11), 1227-1231
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We designed and synthesized a new series of prodrug-type anti-HIV agents consisting of a peptidomimetic HIV protease inhibitor conjugated with a nucleoside reverse transcriptase inhibitor in an effort to enhance the antiviral activity. For the conjugation, a series of linkers that conjoin the two different classes of inhibitors have been investigated. Conjugates using a succinyl amino acid linker were shown to release the parent components via the spontaneous imide formation at a faster rate compared to conjugates using a glutaryl amino acid linker, as expected from the energetically favorable cyclization to the five-membered ring. Herein, we report a new "double-drug" (KNI-1039 conjugated to AZT) with a glutarylglycine linker, which exhibited extremely potent anti-HIV activity compared with that of the individual components.

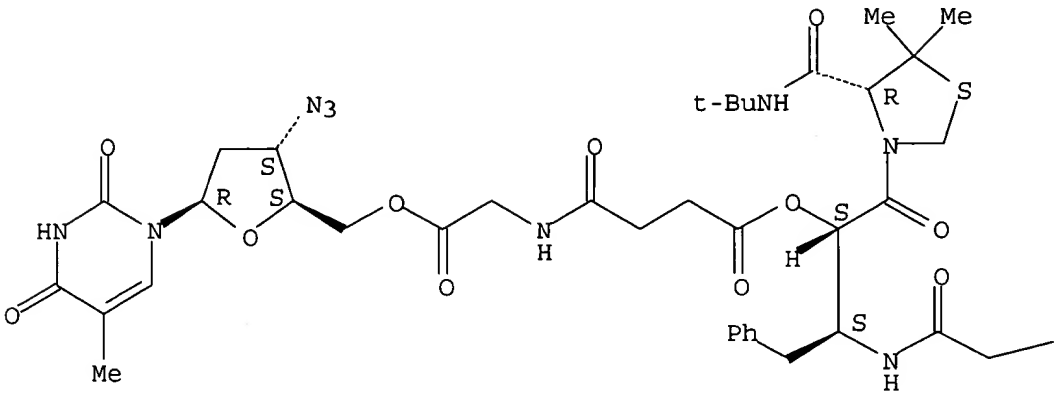
IT **288399-75-7P**, KNI 1038 **288399-76-8P**, KNI 1039
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(anti-HIV activity of prodrug form of HIV protease inhibitor conjugated with a reverse transcriptase inhibitor by a spontaneously cleavable linker)

RN 288399-75-7 HCAPLUS
CN Glycine, N-[4-[(1S,2S)-1-[[(4R)-4-[[(1,1-dimethylethyl)amino]carbonyl]-5,5-dimethyl-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-

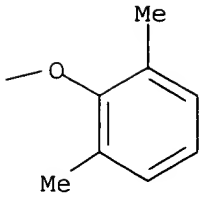
3-phenylpropoxy]-1,4-dioxobutyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



PAGE 1-B

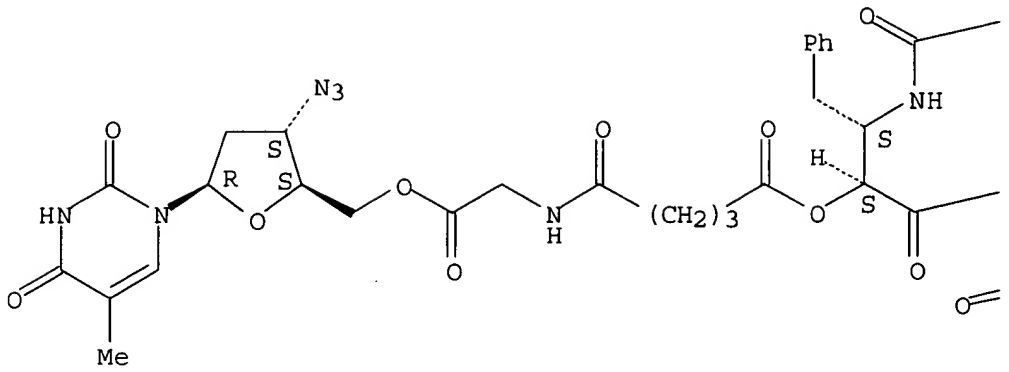


RN 288399-76-8 HCAPLUS

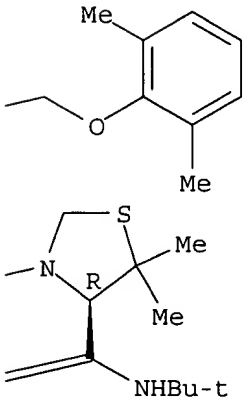
CN Glycine, N-[5-[(1S,2S)-1-[[(4R)-4-[[(1,1-dimethylethyl)amino]carbonyl]-5,5-dimethyl-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,5-dioxopentyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 19 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:264480 HCAPLUS
DOCUMENT NUMBER: 133:171819
TITLE: New type prodrugs of anti-HIV agents consisting of the HIV protease inhibitor and reverse transcriptase inhibitor
AUTHOR(S): Matsumoto, Hikaru; Kimura, Tooru; Hamawaki, Tomonori; Kiso, Yoshiaki
CORPORATE SOURCE: Department of Medicinal Chemistry, Kyoto Pharmaceutical University, Kyoto, 607-8412, Japan
SOURCE: Peptide Science (1999), 36th, 187-188
CODEN: PSCIFQ; ISSN: 1344-7661
PUBLISHER: Japanese Peptide Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A new series of anti-HIV agents, conjugate of the HIV protease inhibitor

and reverse transcriptase inhibitor, was investigated in an effort to enhance the antiviral activity of HIV protease inhibitors. For the conjugation, a series of linkers that connect the hydroxyl groups of the HIV protease inhibitor and the reverse transcriptase inhibitor were examined Among them, the prodrug with glutarylglycine linker exhibited the most potent anti-HIV activity.

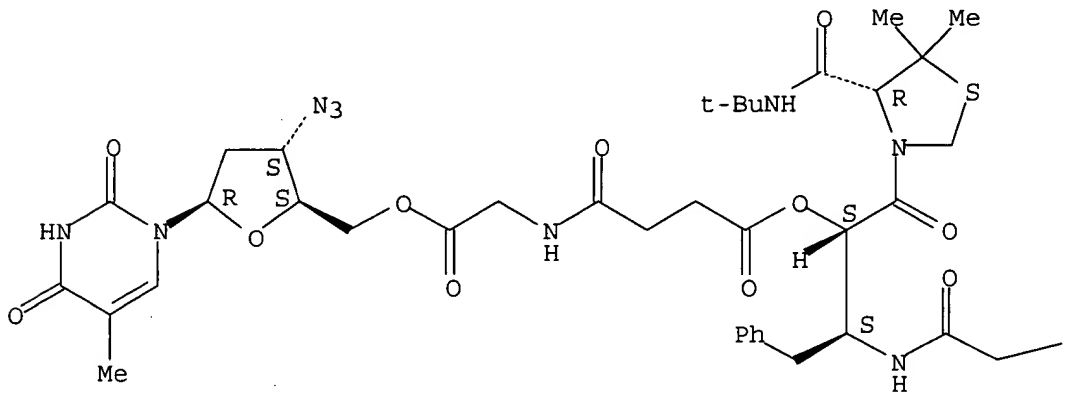
IT **288399-75-7**, KNI 1038 **288399-76-8**, KNI 1039
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(prodrugs of anti-HIV agents consisting of the HIV protease inhibitor and reverse transcriptase inhibitor)

RN 288399-75-7 HCAPLUS

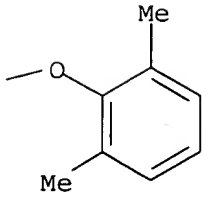
CN Glycine, N-[4-[(1S,2S)-1-[[(4R)-4-[[(1,1-dimethylethyl)amino]carbonyl]-5,5-dimethyl-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,4-dioxobutyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



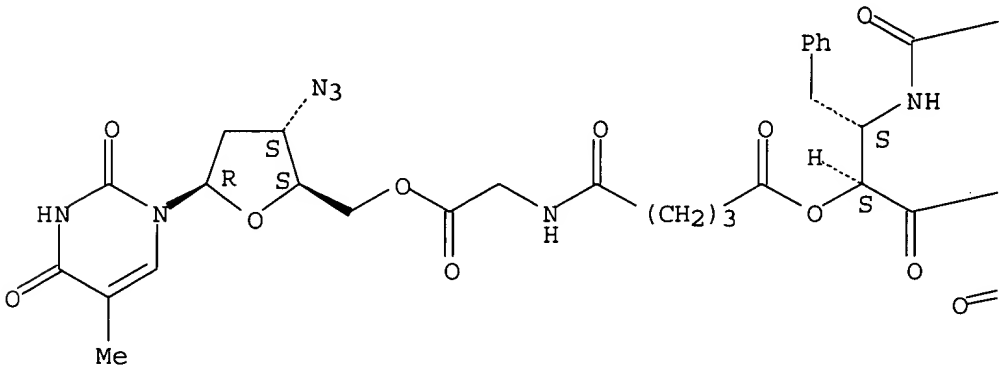
PAGE 1-B



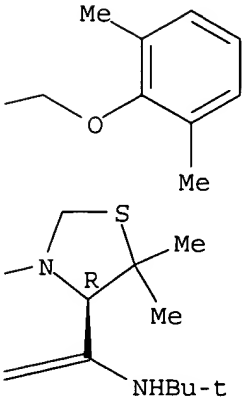
RN 288399-76-8 HCAPLUS
CN Glycine, N-[5-[(1S,2S)-1-[[(4R)-4-[[(1,1-dimethylethyl)amino]carbonyl]-5,5-dimethyl-3-thiazolidinyl]carbonyl]-2-[[(2,6-dimethylphenoxy)acetyl]amino]-3-phenylpropoxy]-1,5-dioxopentyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 20 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:211177 HCAPLUS
DOCUMENT NUMBER: 131:35751
TITLE: Designing prodrugs for the hPEPT1 transporter
AUTHOR(S): Han, Hyo-Kyung; Rhie, Julie K.; Oh, Doo-Man; Amidon, Gordon L.
CORPORATE SOURCE: College of Pharmacy, The University of Michigan, Ann Arbor, MI, 48109-1065, USA
SOURCE: Polymer Preprints (American Chemical Society, Division

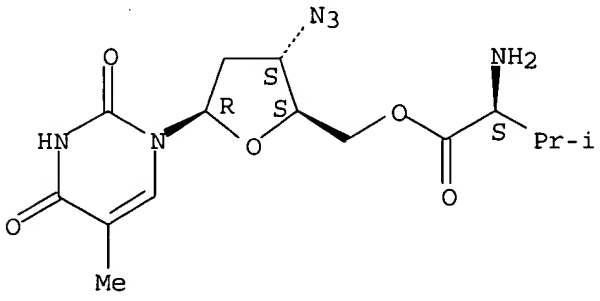
of Polymer Chemistry) (1999), 40(1), 259-260
CODEN: ACPPAY; ISSN: 0032-3934
PUBLISHER: American Chemical Society, Division of Polymer Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It is shown that amino acid ester prodrugs can be a good approach to targeting a peptide transporter for improving oral drug absorption of polar nucleoside analogs. A new rationale is provided in the prodrug strategy of targeting a peptide transporter via the non-peptidyl amino acid esters. 5'-Amino acid ester prodrugs of acyclovir and AZT were prepared and studied.

IT **128305-57-7**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(designing prodrugs of acyclovir and AZT for the hPEPT1 transporter)

RN 128305-57-7 HCAPLUS
CN L-Valine, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 21 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:618282 HCAPLUS
DOCUMENT NUMBER: 129:325705

TITLE: Cellular uptake mechanism of amino acid ester prodrugs in Caco-2/hPEPT1 cells overexpressing a human peptide transporter

AUTHOR(S): Han, Hyo-Kyung; Oh, Doo-Man; Amidon, Gordon L.
CORPORATE SOURCE: College of Pharmacy, The University of Michigan, Ann Arbor, MI, 48109-1065, USA

SOURCE: Pharmaceutical Research (1998), 15(9), 1382-1386
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Plenum Publishing Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study characterized the cellular uptake mechanism and hydrolysis of the amino acid ester prodrugs of nucleoside antiviral drugs in the transiently transfected Caco-2 cells overexpressing a human intestinal peptide transporter, hPEPT1 (Caco-2/hPEPT1 cells). Amino acid ester prodrugs of acyclovir and AZT were synthesized and their apical membrane permeability and hydrolysis were evaluated in Caco-2/hPEPT1 cells. The cellular uptake mechanism of prodrugs was investigated through the competitive inhibition study in Caco-2/hPEPT1 cells. L-valyl ester of acyclovir (L-Val-ACV) was approx. ten fold more permeable across the

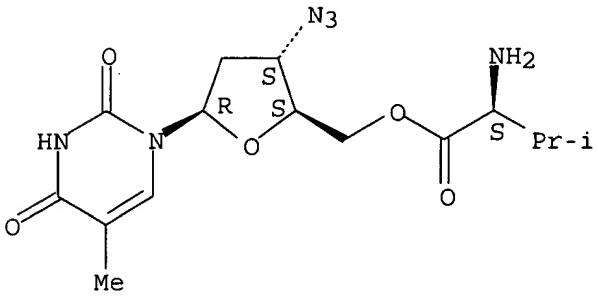
apical membrane than acyclovir and four times more permeable than D-valyl ester of acyclovir (D-Val-ACV). Correspondingly, L-valyl ester of AZT (L-Val-AZT) exhibited three fold higher cellular uptake than AZT. Therefore, amino acid ester prodrugs significantly increased the cellular uptake of the parent drugs and exhibited the D,L-stereoselectivity. Furthermore, prodrugs were rapidly hydrolyzed to the parent drugs by the intracellular hydrolysis, following the apical membrane transport. In the inhibition studies, cephalexin and small dipeptides strongly inhibited the cellular uptake of L-Val-ACV while L-valine had no effect, indicating that the peptide transporter is primarily responsible for the apical membrane transport of L-Val-ACV. In addition, the cellular uptake of L-Val-ACV was five times higher in Caco-2/hPEPT1 cells than the uptake in the untransfected Caco-2 cells, implying the cellular uptake of L-Val-ACV was related to the enhancement of the peptide transport activity in Caco-2/hPEPT1 cells. Caco-2/hPEPT1 system is an efficient in vitro model for the uptake study of peptidyl derivs. Amino acid ester prodrugs significantly improved the cellular uptake of the parent drugs via peptide transport mechanism and were rapidly converted to the active parent drugs by the intracellular hydrolysis.

IT **128305-57-7**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cellular uptake mechanism of amino acid ester prodrugs in Caco-2/hPEPT1 cells overexpressing a human peptide transporter)

RN 128305-57-7 HCAPLUS

CN L-Valine, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 22 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:518430 HCAPLUS

DOCUMENT NUMBER: 129:250185

TITLE: 5'-Amino acid esters of antiviral nucleosides, acyclovir, and AZT are absorbed by the intestinal PEPT1 peptide transporter

AUTHOR(S): Han, Hyo-Kyung; De Vrueh, Remco L. A.; Rhie, Julie K.; Covitz, Kuang-Ming Y.; Smith, Philip L.; Lee, Chao-Pin; Oh, Doo-Man; Sadee, Wolfgang; Amidon, Gordon L.

CORPORATE SOURCE: College of Pharmacy, The University of Michigan, MI, 48109-1065, USA

SOURCE: Pharmaceutical Research (1998), 15(8), 1154-1159
CODEN: PHREEB; ISSN: 0724-8741

PUBLISHER: Plenum Publishing Corp.

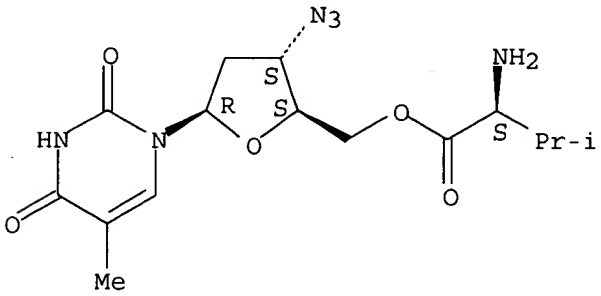
DOCUMENT TYPE: Journal
LANGUAGE: English

AB General use of nucleoside analogs in the treatment of viral infections and cancer is often limited by poor oral absorption. Valacyclovir, a water soluble amino acid ester prodrug of acyclovir has been reported to increase the oral bioavailability of acyclovir but its absorption mechanism is unknown. This study characterized the intestinal absorption mechanism of 5'-amino acid ester prodrugs of the antiviral drugs and examined the potential of amino acid esters as an effective strategy for improving oral drug absorption. Acyclovir (ACV) and Zidovudine (AZT) were selected as the different sugar-modified nucleoside antiviral agents and synthesized to L-valyl esters of ACV and AZT (L-Val-ACV and L-Val-AZT), D-valyl ester of ACV (D-Val-ACV) and glycyl ester of ACV (Gly-ACV). The intestinal absorption mechanism of these 5'-amino acid ester prodrugs was characterized in three different exptl. systems: in situ rat perfusion model, CHO/hPEPT1 cells and Caco-2 cells. Testing 5'-amino acid ester prodrugs of acyclovir and AZT, the authors found that the prodrugs increased the intestinal permeability of the parent nucleoside analog 3-to 10-fold. The dose- dependent permeation enhancement was selective for the L-amino acid esters. Competitive inhibition studies in rats and in CHO cells transfected with the human peptide transporter, hPEPT1, demonstrated that membrane transport of the prodrugs was mediated predominantly by the PEPT1 H+ H+/dipeptide cotransporter even though these prodrugs did not possess a peptide bond. Finally, transport studies in Caco-2 cells confirmed that the 5'-amino acid ester prodrugs enhanced the transcellular transport of the parent drug. This study demonstrates that L-amino acid-nucleoside chimeras can serve as prodrugs to enhance intestinal absorption via the PEPT1 transporter, providing a novel strategy for improving oral therapy of nucleoside drugs.

IT **128305-57-7P**
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(5'-amino acid esters of antiviral nucleosides (acyclovir and AZT) are absorbed by intestinal PEPT1 peptide transporter)

RN 128305-57-7 HCAPLUS
CN L-Valine, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 23 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:731868 HCAPLUS
DOCUMENT NUMBER: 126:1184
TITLE: MDP derivatives and conjugates having hematopoietic

function stimulating activity
INVENTOR(S): Bahr, Georges; Lefrancier, Pierre; Chedid, Louis
PATENT ASSIGNEE(S): Vacsyn S.A., Fr.
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9631533	A1	19961010	WO 1996-FR527	19960405
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
FR 2732604	A1	19961011	FR 1995-4194	19950407
FR 2732604	B1	19970606		
CA 2216599	AA	19961010	CA 1996-2216599	19960405
AU 9655046	A1	19961023	AU 1996-55046	19960405
EP 819136	A1	19980121	EP 1996-912079	19960405
EP 819136	B1	20020130		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11503426	T2	19990326	JP 1996-530052	19960405
AT 212644	E	20020215	AT 1996-912079	19960405
PT 819136	T	20020731	PT 1996-912079	19960405
ES 2171665	T3	20020916	ES 1996-912079	19960405
US 6267968	B1	20010730	US 1999-302145	19990429

PRIORITY APPLN. INFO.:	FR 1995-4194	A 19950407
	WO 1996-FR527	W 19960405
	US 1997-930862	A3 19971007

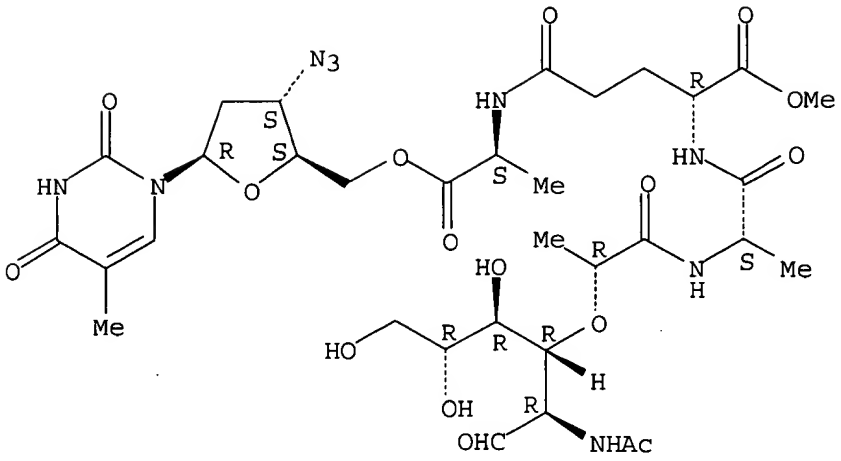
OTHER SOURCE(S): MARPAT 126:1184

AB A pharmaceutical composition for stimulating the hematopoietic function and preventing the myelotoxic side-effects of some treatments, contain at least one water-soluble muramyl peptide derivative such as Muradimetide (I) or muroctasine. I.v. administration of 25 mg I/kg to guinea pigs for 4 days increased the number of myelocytes from 7x104/mL to 72x104/mL. A solution of 320 mg 6-O-succinyl-N-acetyl-muramyl-L-alanyl-D-glutamic acid di-Me ester in 10 mL anhydrous DMF was mixed with 0.05 mL of Me morpholine, 0.06 mL of iso-Bu chlorocarbaonate, and 267 mg 3'-azido-3'-deoxythymidine and stirred at 15° for 24 h to obtain 6-O-(succinyl-3'-azido-3'-deoxythymidine)-N-acetyl-muramyl-L-alanyl-D-glutamic acid di-Me ester which was purified (yield:50%).

IT **183796-09-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(MDP derivs. and conjugates having hematopoietic function stimulating activity)

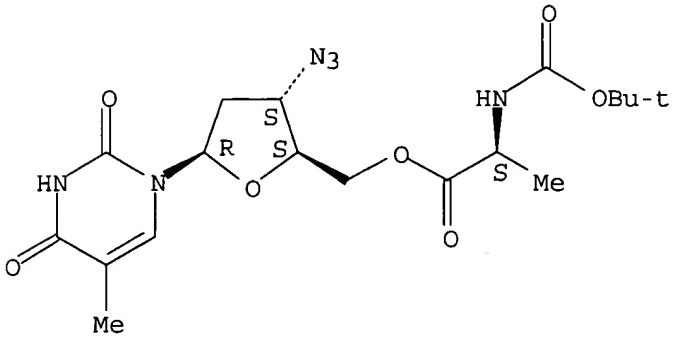
RN 183796-09-0 HCAPLUS
CN L-Alanine, N-(N-acetylmuramoyl)-L-alanyl-D-γ-glutamyl-, 2-methyl ester, 3-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



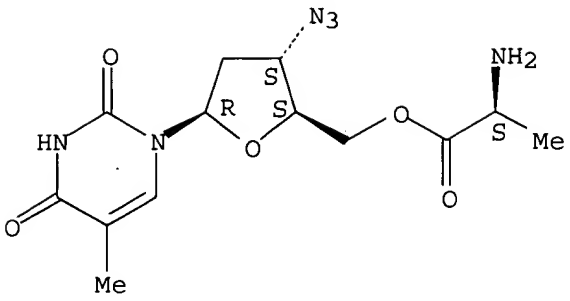
IT **183796-11-4P 183904-91-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(MDP derivs. and conjugates having hematopoietic function stimulating activity)
RN 183796-11-4 HCAPLUS
CN L-Alanine, N-[(1,1-dimethylethoxy)carbonyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 183904-91-8 HCAPLUS
CN L-Alanine, 5'-ester with 3'-azido-3'-deoxythymidine, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L12 ANSWER 24 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:643919 HCAPLUS
DOCUMENT NUMBER: 125:284912
TITLE: Liposome composition and method for administering drugs having reactive hydroxyl group
INVENTOR(S): Woodle, Martin C.; Zalipsky, Samuel; Martin, Francis J.
PATENT ASSIGNEE(S): Sequus Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9625147	A1	19960822	WO 1996-US2005		19960214
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT					
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
AU 9649818	A1	19960904	AU 1996-49818		19960214
PRIORITY APPLN. INFO.:			US 1995-388374	A	19950214
			WO 1996-US2005	W	19960214

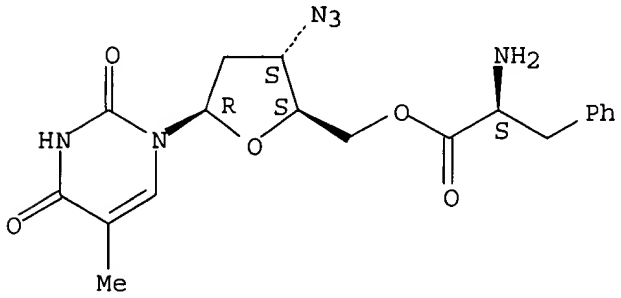
AB A liposome composition and method of use in administering a compound having a reactive hydroxyl group to a selected in vivo site are disclosed. The composition includes a suspension of liposomes having an inside/outside pH gradient, and a conjugate of the compound with an adduct effective to maintain the compound in liposome-encapsulated form in response to the pH gradient. The 5'-OH function of AZT was esterified by reaction with various N-protected amino acids (lysine, phenylalanine, β-alanine, glycine and 6-aminocaproic acid). The reaction mixture contained 1.0 equivalent of AZT, 1.1 equivalent of t-BOC amino acid, 1.2 equivalent of dicyclohexylcarbodiimide as a condensing agent, and 1.5 equivalent of 4-dimethylaminopyridine as a catalyst in EtOAc. Yields of the AZT-amino acid esters formed ranged from 50-85%. The AZT-amino acid esters were

loaded in long-circulating liposomes prepared from polyethylene glycol-conjugated phosphatidylethanolamine, partially hydrogenated soya phosphatidylcholine, and cholesterol (1:3:1).

IT **125780-79-2P 125780-83-8P 182560-18-5P 182560-19-6P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(liposome compns. for administering drugs having reactive hydroxyl group)

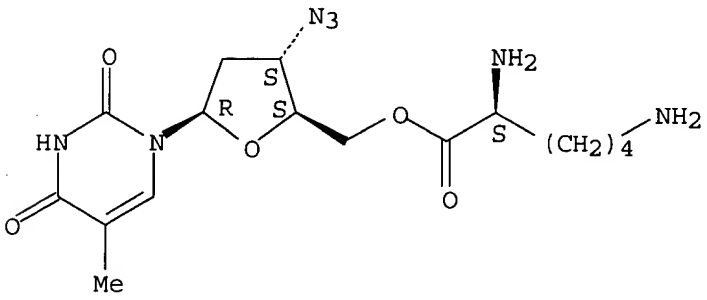
RN 125780-79-2 HCAPLUS
CN L-Phenylalanine, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



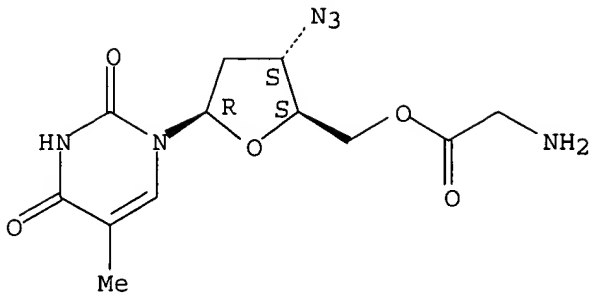
RN 125780-83-8 HCAPLUS
CN L-Lysine, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



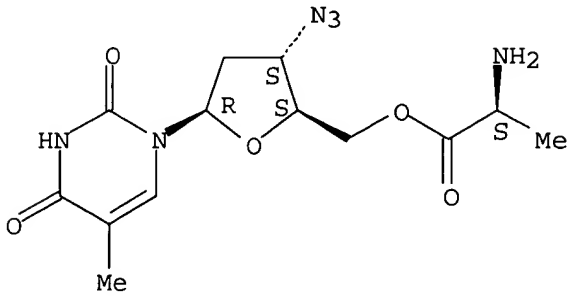
RN 182560-18-5 HCAPLUS
CN Glycine, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 182560-19-6 HCAPLUS
CN L-Alanine, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 25 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:297141 HCAPLUS
DOCUMENT NUMBER: 123:187729
TITLE: Inhibition of infection of T-cells with human immunodeficiency virus type 1 by dideoxynucleosides conjugated with oligopeptides
AUTHOR(S): Shimizu, N. S.; Handa, A.; Shimizu, N. G.; Ikeda, R.; Uchiyama, T.; Achiwa, K.; Hoshino, H.
CORPORATE SOURCE: Dep. Hyg. Virol., Gunma Univ. Sch. Med., Gunma, 371, Japan
SOURCE: Antiviral Chemistry & Chemotherapy (1995), 6(1), 17-24
CODEN: ACCHEH; ISSN: 0956-3202
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We conjugated nucleoside derivs. that have anti-HIV-1 activities with oligopeptides that should bind to the gp120 of the HIV-1 virion, and examined their anti-HIV-1 activities. These derivates included 3'-azido-2',3'-dideoxythymidine (AZT), 2',3'-dideoxyinosine (ddU), 2',3'-dideoxycytidine (ddC), 2',3'-dideoxyinosine (ddI) and 2',3'-dideoxyadenine (ddA). Dipeptides consisting of N-carbomethoxy-carbonyl-prolyl-phenylalanyl-benzyl ester (CPF) and oligopeptides derived from the complementarity-determining region 2 (CDR2) of domain 1 of CD4 were synthesized. The N-terminals of these peptides were conjugated with the 5'OH of AZT, ddU, ddC, ddI, or ddA through carbonyl moieties. CPF conjugated with AZT, ddC, ddI or ddA through two-carbonyl moieties exhibited powerful anti-HIV-1 activity, which was similar to that of the resp. nucleosides when compared at the same molar concentration No complex

compound connected by a one-carbonyl moiety had anti-HIV-1 activity, whereas a tetrapeptide or octapeptide of the CDR2 region combined with AZT did not have such activity. The toxicity of these CPF-containing compds. to human peripheral blood lymphocytes was slightly weaker than the toxicities of the corresponding nucleosides lacking CPF. Antiviral nucleosides containing oligopeptides may be used as lead compds. in an effort to isolate more effective and less cytotoxic anti-HIV-1 agents.

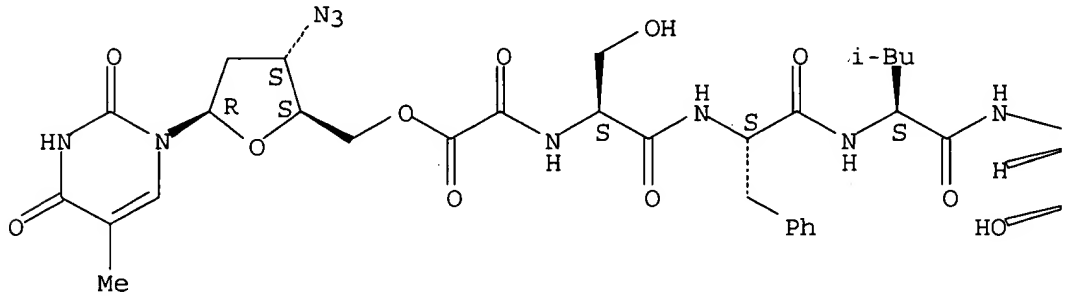
IT **139300-60-0 167699-62-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HIV-1 inhibition in T-cells by dideoxynucleosides conjugated with oligopeptides)

RN 139300-60-0 HCAPLUS

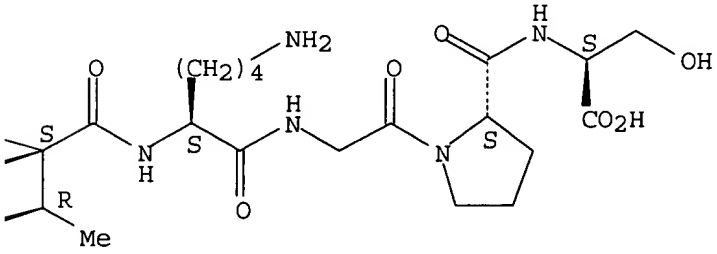
CN L-Serine, N-[1-[N-[N2-[N-[N-[N-[N-(carboxycarbonyl)-L-seryl]-L-phenylalanyl]-L-leucyl]-L-threonyl]-L-lysyl]glycyl]-L-prolyl]-, N-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

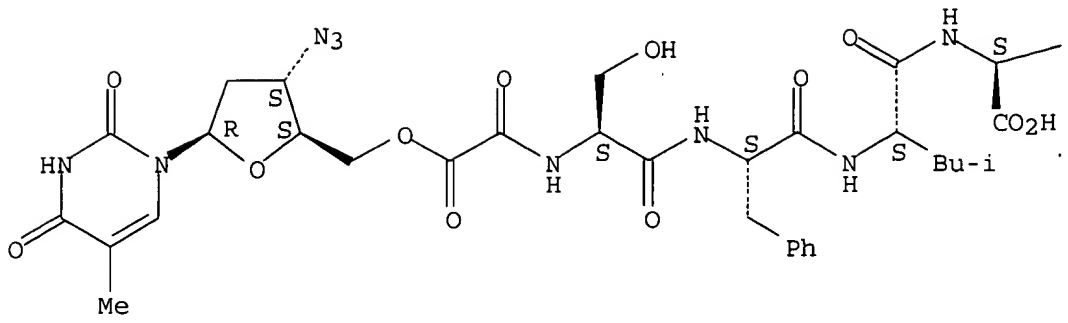


RN 167699-62-9 HCAPLUS

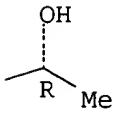
CN L-Threonine, N-[N-[N-[N-[(3'-azido-3'-deoxythymidin-5'-O-yl)oxoacetyl]-L-seryl]-L-phenylalanyl]-L-leucyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L12 ANSWER 26 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:229213 HCAPLUS
DOCUMENT NUMBER: 122:10363
TITLE: Preparation of prodrug esters
INVENTOR(S): Budt, Karl-Heinz; Peyman, Anuschirwan
PATENT ASSIGNEE(S): Hoechst A.-G., Germany
SOURCE: Ger. Offen., 29 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4308095	A1	19940915	DE 1993-4308095	19930313

PRIORITY APPLN. INFO.: DE 1993-4308095 19930313
OTHER SOURCE(S): MARPAT 122:10363

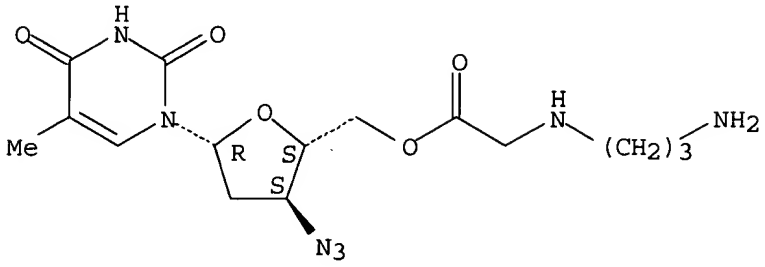
AB W(R5)a [I; R5 = e.g., O2C(CR11R12)sX(CR15R16)lNR21[(CR15R16)mNR21]oR24; R11,R12,R15,R16 = H or alkyl; R21 = H, (cyclo)alkyl, alkoxycarbonyl; R24 = H, (cyclo)alkyl, alkenyl, aryl, etc.; W = mono-, di-, or tri-dehydroxylated drug residue; X = O, S, (alkyl)imino, etc.; a = 1-3; l = 2 or 3; o = 0-3; s = 1-5] were prepared Thus, testosterone was bromoacetylated and the product condensed with MeNHCH2CH2NMeCO2CMe3 (preparation given) to give, after deprotection, I (R5 = O2CCH2NMeCH2CH2NHMe, W = dehydroxylated testosterone residue, a= 1).

IT **159457-55-3P 159457-56-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of prodrug esters)

RN 159457-55-3 HCAPLUS
CN Glycine, N-(3-aminopropyl)-, 5'-ester with 3'-azido-3'-deoxythymidine,

hydrochloride (9CI) (CA INDEX NAME)

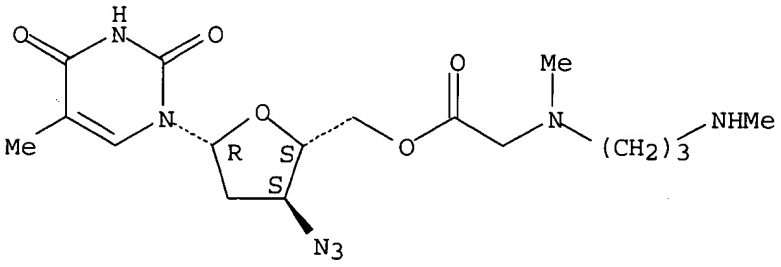
Absolute stereochemistry.



●x HCl

RN 159457-56-4 HCAPLUS
CN Glycine, N-methyl-N-[3-(methylamino)propyl]-, 5'-ester with 3'-azido-3'-deoxythymidine, hydrochloride (9CI) (CA INDEX NAME)

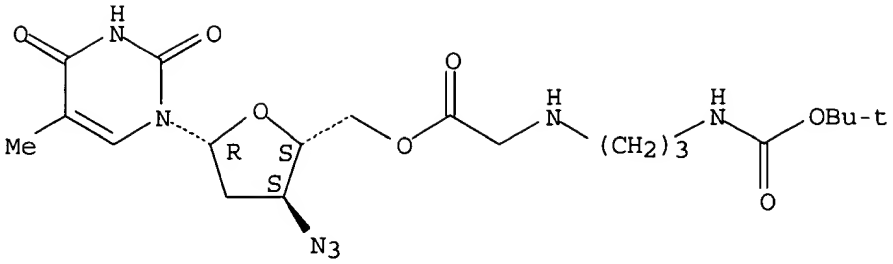
Absolute stereochemistry.



●x HCl

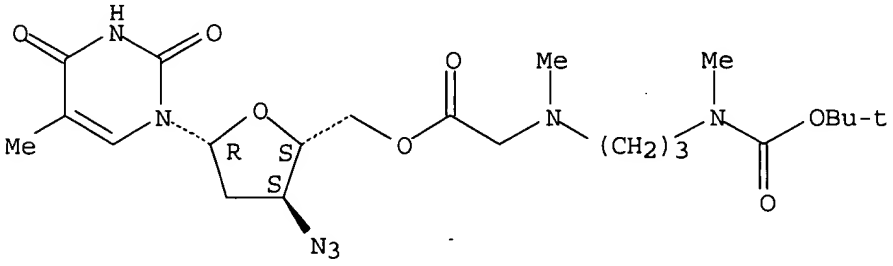
IT **159457-62-2P 159457-63-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of prodrug esters)
RN 159457-62-2 HCAPLUS
CN Glycine, N-[3-[[(1,1-dimethylethoxy)carbonyl]amino]propyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

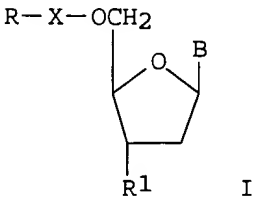


RN 159457-63-3 HCAPLUS
CN Glycine, N-[3-[[(1,1-dimethylethoxy)carbonyl]methylamino]propyl]-N-methyl-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 27 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:271121 HCAPLUS
DOCUMENT NUMBER: 120:271121
TITLE: Synthesis of peptide derivatives potent to gp120, having 2',3'-dideoxynucleoside, and their anti-HIV activity
AUTHOR(S): Uchiyama, Yaketo; Achiwa, Kazuo
CORPORATE SOURCE: Sch. Pharm. Sci., Univ. Shizuoka, Shizuoka, 422, Japan
SOURCE: Pept. Chem. 1992, Proc. Jpn. Symp., 2nd (1993), Meeting Date 1992, 703-6. Editor(s): Yanaihara, Noboru. ESCOM: Leiden, Neth.
CODEN: 59NTAC
DOCUMENT TYPE: Conference
LANGUAGE: English
GI



I

AB A report from a symposium on the prepn and human immunodeficiency virus (HIV) inhibitory activity of peptide-deoxynucleoside conjugates I (R =

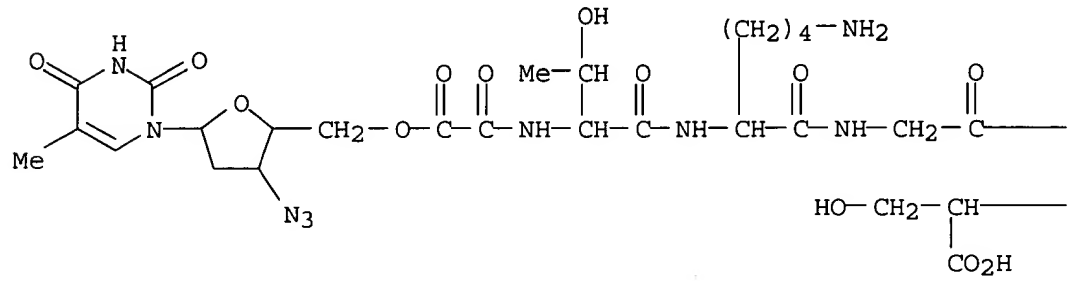
Ser-Phe-Leu-Thr-Lys-Gly-Pro-Ser-OH, Thr-Lys-Gly-Pro-Ser-OH, Pro-D-Phe-OCH2Ph, R1 = H, N3, B = thymine, uracil, cytosine, adenine, hypoxanthine, X = COCO, CO, COCH2CH2CO).

IT **154566-66-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and immunodeficiency virus inhibitory activity of)

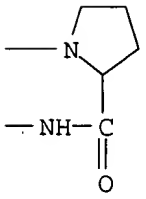
RN 154566-66-2 HCAPLUS

CN L-Serine, N-[1-[N-[N2-[N-(carboxycarbonyl)-L-threonyl]-L-lysyl]glycyl]-L-prolyl]-, N-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



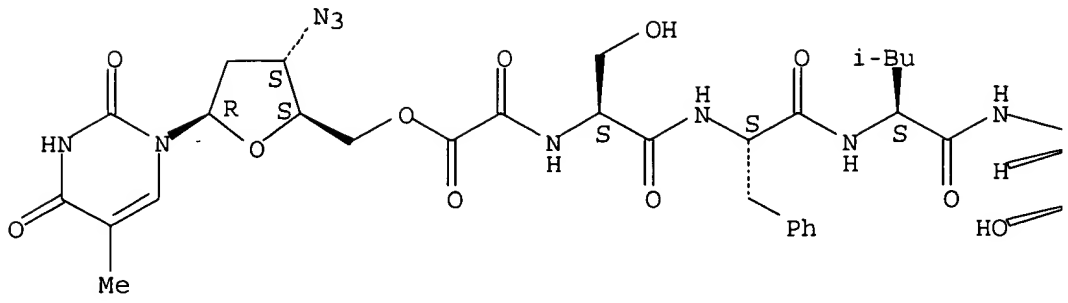
IT **139300-60-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 139300-60-0 HCAPLUS

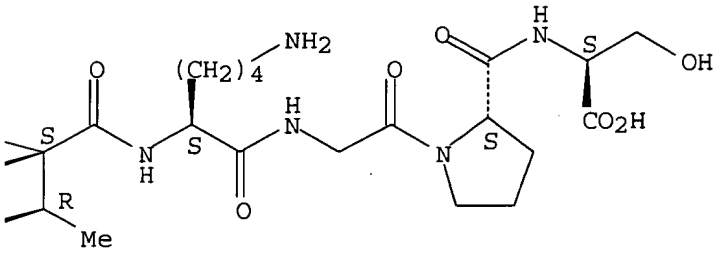
CN L-Serine, N-[1-[N-[N2-[N-[N-[N-[N-(carboxycarbonyl)-L-seryl]-L-phenylalanyl]-L-leucyl]-L-threonyl]-L-lysyl]glycyl]-L-prolyl]-, N-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



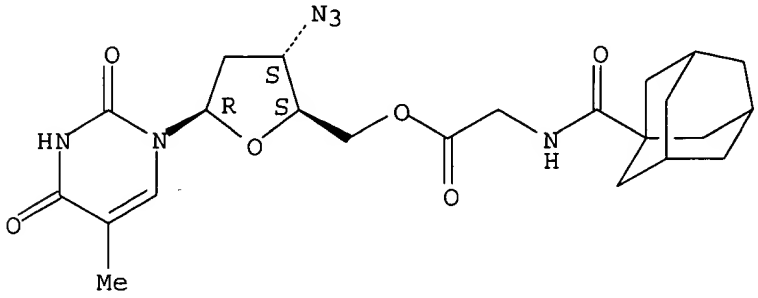
L12 ANSWER 28 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:226716 HCAPLUS
DOCUMENT NUMBER: 120:226716
TITLE: Adamantane as a brain-directed drug carrier for poorly absorbed drug. 2. AZT derivatives conjugated with the 1-adamantane moiety
AUTHOR(S): Tsuzuki, Noriko; Hama, Teruo; Kawada, Mitsuhiro; Hasui, Akihiro; Konishi, Ryoji; Shiwa, Satoshi; Ochi, Yoshihito; Futaki, Shiroh; Kitagawa, Kouki
CORPORATE SOURCE: Teikoku Seiyaku Co., Ltd., Ochi, 769-26, Japan
SOURCE: Journal of Pharmaceutical Sciences (1994), 83(4), 481-4
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Five AZT (azidothymidine) prodrugs conjugated with the 1-adamantane moiety via an an ester bond were prepared to improve the transport of AZT into the central nervous system (CNS). In in vitro degradation studies with rat and human plasma, it was demonstrated that the prodrugs were degraded enzymically and converted quant. to their parent drug, AZT. As assessed by octanol-buffer partitioning, the prodrugs were much more lipophilic than AZT and were expected to penetrate the blood-brain barrier (BBB) readily. In in vivo studies, in which the prodrugs were administered i.v. to rats, the prodrugs in brain tissue were detected at 7-18-fold higher concns. than AZT in spite of the negligible amount of the prodrug in the cerebrospinal fluid. Thus, the introduction to AZT of the 1-adamantane moiety results in the enhancement of the BBB penetration. This pharmaceutical approach would be beneficial for the efficient treatment of the CNS infection by human immuno-deficiency virus.

IT **139143-34-3P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and enzymic hydrolysis and blood-brain barrier penetration of)
RN 139143-34-3 HCAPLUS
CN Glycine, N-(tricyclo[3.3.1.13,7]dec-1-ylcarbonyl)-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

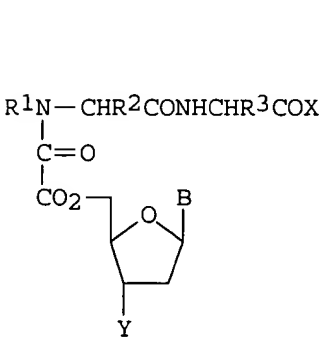
Absolute stereochemistry.



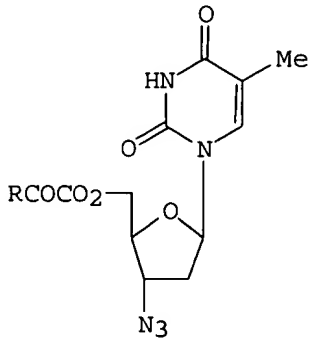
L12 ANSWER 29 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:581251 HCAPLUS
DOCUMENT NUMBER: 119:181251
TITLE: Preparation of peptide derivatives of dideoxynucleoside as anti-HIV agents
INVENTOR(S): Achinami, Kazuo; Hoshino, Koro
PATENT ASSIGNEE(S): Fuji Yakuhin Kogyo Kk, Japan; Achinami Kazuo; Hoshino Koro
SOURCE: Jpn. Kokai Tokkyo Koho, 11 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 05086096	A2	19930406	JP 1991-320125	19910928

PRIORITY APPLN. INFO.: JP 1991-320125 19910928
OTHER SOURCE(S): MARPAT 119:181251
GI



I



II

AB The title compds. [I; R1 = H and R2 = alkyl, HOCH2; or R1R2 = (CH2)n wherein n = 3,4; R3 = (un)substituted CH2Ph; X = lower alkoxy, PhCH2O, amino acid or peptide derivative; Y = H, N3; B = nucleic acid base], useful for the treatment of AIDS, are prepared Thus, esterification of AZT with p-nitrophenyloxalyl chloride in the presence of Et3N in THF followed by condensation with H-Pro-Phe-OCH2Ph in the presence of 4-dimethylaminopyridine in DMF gave an AZT ester (II; R = Pro-Phe-OCH2Ph) (III). III at 0.3 μg/mL in vitro showed <1% the expression of HIV antigens in MT-cells infected with HIV vs. 50% for the control. Addnl. 7 I were prepared

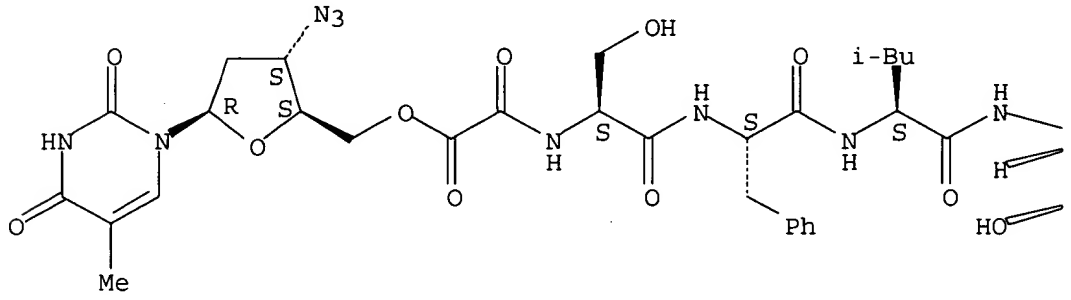
IT **139300-60-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as anti-HIV agent)

RN 139300-60-0 HCAPLUS

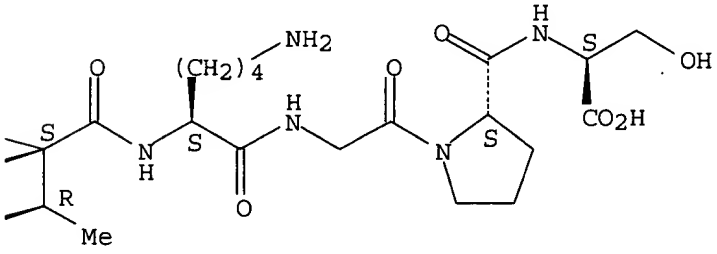
CN L-Serine, N-[1-[N-[N2-[N-[N-[N-[N-(carboxycarbonyl)-L-seryl]-L-phenylalanyl]-L-leucyl]-L-threonyl]-L-lysyl]glycyl]-L-prolyl]-, N-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

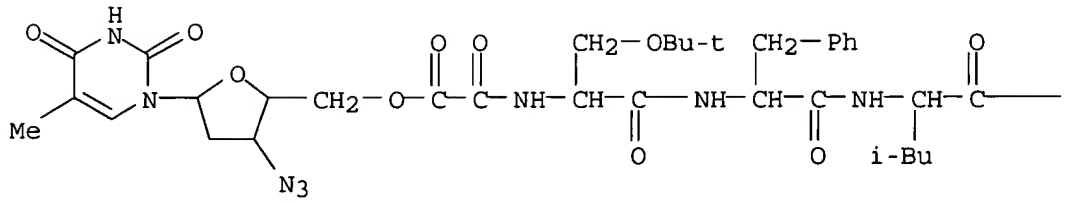


IT **139300-59-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for anti-HIV dideoxynucleoside peptide derivative)

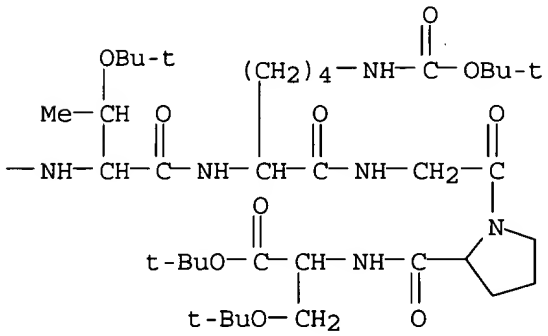
RN 139300-59-7 HCAPLUS

CN L-Serine, N-[1-[N-[N2-[N-[N-[N-[N-(carboxycarbonyl)-O-(1,1-dimethylethyl)-L-seryl]-L-phenylalanyl]-L-leucyl]-O-(1,1-dimethylethyl)-L-threonyl]-N6-[(1,1-dimethylethoxy)carbonyl]-L-lysyl]glycyl]-L-prolyl]-O-(1,1-dimethylethyl)-, 1-(1,1-dimethylethyl) ester, N-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



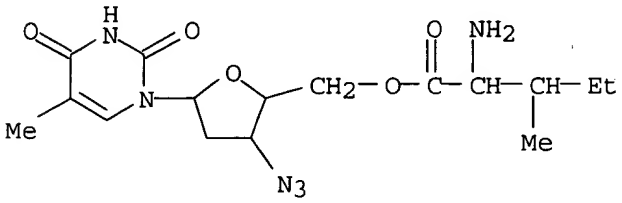
L12 ANSWER 30 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:440196 HCAPLUS
DOCUMENT NUMBER: 119:40196
TITLE: Comparative pharmacokinetics of two prodrugs of zidovudine in rabbits: enhanced levels of zidovudine in brain tissue
AUTHOR(S): Lupia, Raul H.; Ferencz, Nicholas; Lertora, Juan J. L.; Aggarwal, Sunil K.; George, William J.; Agrawal, Krishna C.
CORPORATE SOURCE: Sch. Med., Tulane Univ., New Orleans, LA, 70112, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1993), 37(4), 818-24
CODEN: AMACCQ; ISSN: 0066-4804
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pharmacokinetics of two prodrugs of zidovudine (AZT), 1,4-dihydro-1-methyl-3-[(pyridylcarbonyl)oxy] ester and isoleucinyl ester (DPAZT and IAZT, resp.), were investigated in a rabbit model to determine their potential utility as drugs against human immunodeficiency virus. Drugs were administered by i.v. infusion over 5 min at doses equal to 10 mg of AZT per kg of body weight The levels of the prodrugs and of released AZT in plasma, cerebrospinal fluid (CSF), and brain were determined by high-performance liquid chromatog. anal. DPAZT disappeared rapidly from plasma, whereas IAZT maintained a sustained level in plasma for up to 4 h. The levels in plasma of AZT released from DPAZT were consistently lower than the levels of AZT released from IAZT or AZT itself. At 75 min after infusion of AZT, DPAZT, and IAZT, the CSF plasma AZT ratios were 0.23, 0.30, and 0.25, while the brain/CSF AZT ratios were 0.32, 0.63, and 0.64, resp. These results indicate that the administration of each of the

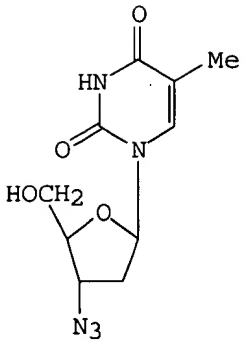
prodrugs produced a higher concentration of AZT in the brain than did the direct
administration of AZT. Both prodrugs therefore may be superior to AZT itself with respect to achieving anti-human immunodeficiency virus concns. within the central nervous system.

IT **125780-95-2**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pharmacokinetics of, zidovudine formation and brain levels in)

RN 125780-95-2 HCAPLUS
CN L-Isoleucine, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)



L12 ANSWER 31 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:592277 HCAPLUS
DOCUMENT NUMBER: 117:192277
TITLE: Synthesis of lipidic peptide conjugates of nucleoside antiviral and cytostatic agents
AUTHOR(S): Hussain, Rohanah; Toth, Istvan; Gibbons, William A.
CORPORATE SOURCE: Sch. Pharm., Univ. London, London, WC1N 1AX, UK
SOURCE: Pept.: Chem. Biol., Proc. Am. Pept. Symp., 12th (1992), Meeting Date 1991, 450-1. Editor(s): Smith, John A.; Rivier, Jean E. ESCOM: Leiden, Neth.
CODEN: 57XGA9
DOCUMENT TYPE: Conference
LANGUAGE: English
GI



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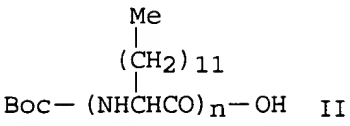
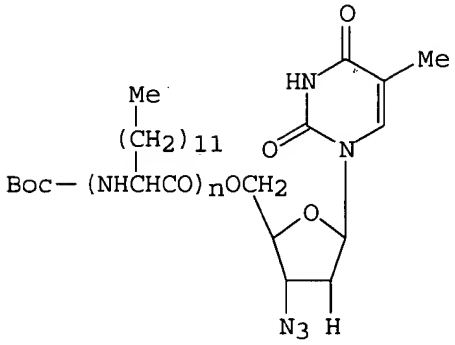


II



III

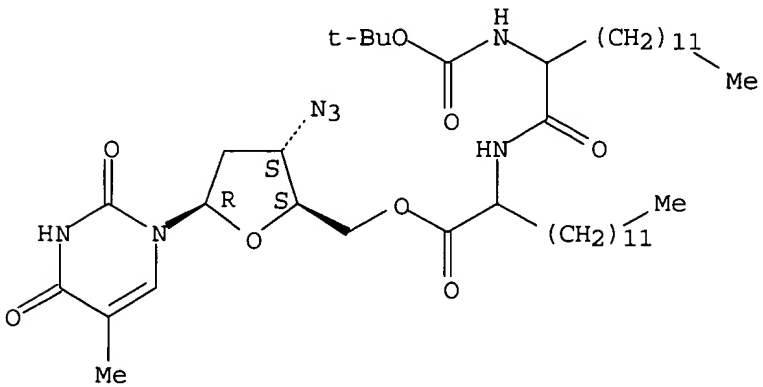
AB A symposium report on the synthesis of lipidic peptide conjugates of AZT (I). The 5'-OH of AZT was condensed with amino acid and oligomers II (Boc = Me3CO2C; n = 1, 2, 3) by water-soluble carbodiimide to give lipophilic conjugates III.

IT **138128-45-7P 138128-46-8P 143900-65-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 138128-45-7 HCAPLUS

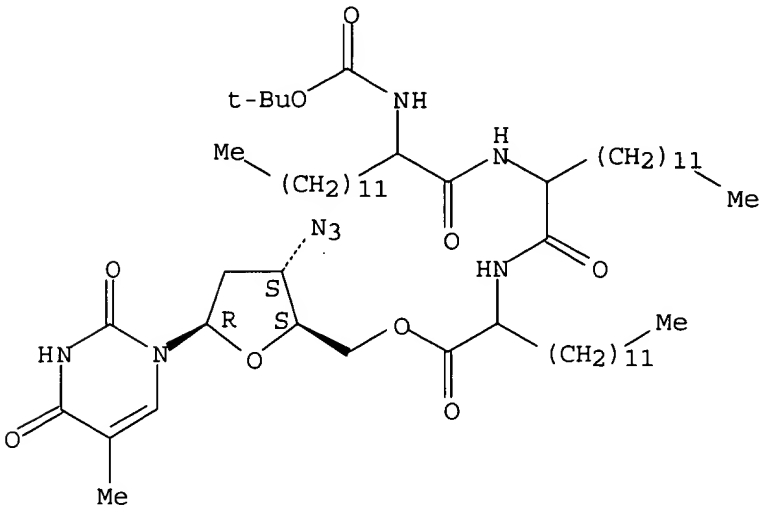
CN Thymidine, 3'-azido-3'-deoxy-, 5'-[2-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxotetradecyl]amino]tetradecanoate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.

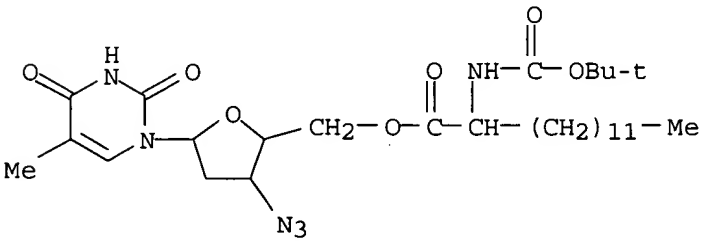


RN 138128-46-8 HCAPLUS
CN Thymidine, 3'-azido-3'-deoxy-, 5'-(2,5,8-tridodecyl-12,12-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatridecanoate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 143900-65-6 HCAPLUS
CN Thymidine, 3'-azido-3'-deoxy-, 5'-[2-[[(1,1-dimethylethoxy)carbonyl]amino] tetradecanoate] (9CI) (CA INDEX NAME)

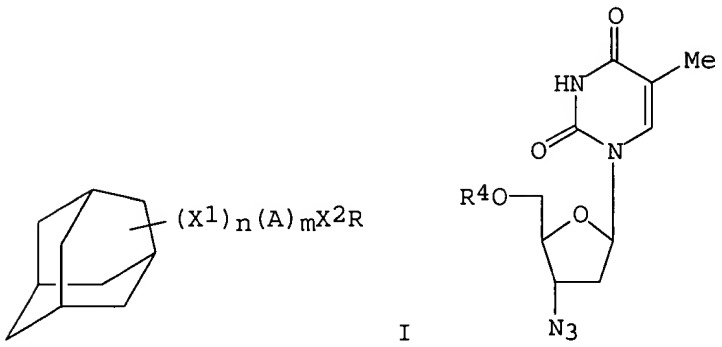


L12 ANSWER 32 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:449260 HCAPLUS
DOCUMENT NUMBER: 117:49260
TITLE: Preparation of adamantylated peptides and other drugs with high blood-brain barrier permeability
INVENTOR(S): Kitagawa, Kouki; Hibi, Toru; Tsuzuki, Noriko
PATENT ASSIGNEE(S): Teikoku Seiyaku Co., Ltd., Japan
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9113081	A1	19910905	WO 1991-JP256		19910227
W: CA, JP, US					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE					
EP 516851	A1	19921209	EP 1991-905340		19910227
EP 516851	B1	19960619			
R: CH, DE, DK, FR, GB, LI, SE					
EP 668290	A1	19950823	EP 1995-105215		19910227
EP 668290	B1	19981111			
R: CH, DE, DK, FR, GB, LI, SE					
US 5652335	A	19970729	US 1994-227997		19940415
PRIORITY APPLN. INFO.:			JP 1990-50116	A	19900228
			EP 1991-905340	A3	19910227
			WO 1991-JP256	W	19910227
			US 1992-920582	B1	19920828

OTHER SOURCE(S): MARPAT 117:49260
GI



I IV

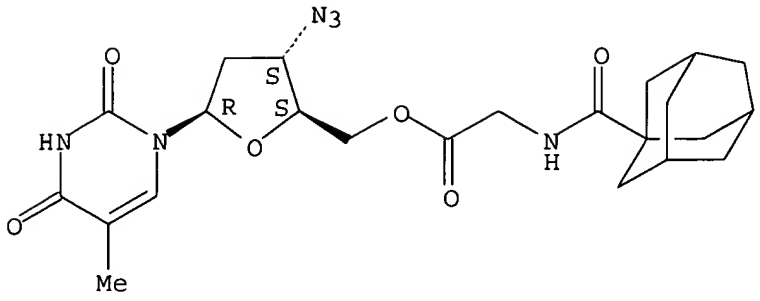
AB The title compds. (I; X1, X2 = ether, urethane, ester, amide bond; A = lower alkylene; when m = 0, n = 0, or when m = 1, n = 0 or 1; R = residue of a physiol. active substance selected from peptides, amino acids, aliphatic amines having a phenolic skeleton, amino sugars, nucleosides, lactam compds., and their derivs., particularly enkephalin, zidovudine, or 2-pyrrolidone), which show high blood-brain barrier permeability and are useful as pharmaceuticals active to the brain, are prepared Thus, hydrogenolysis of Z-Phe-Leu-NHAda (Ada = 1-adamantyl, Z = PhCH2OC) (preparation given) over 5% Pd/C in THF containing AcOH followed by condensation of the azide prepared from Z-Tyr(Bzl)-D-Ala-Gly-R2 (II; R2 = NHNH2, Bzl = PhCH2) (preparation given) in the presence of Et3N in DMF at 0° gave 81% II (R2 = Phe-Leu-NHAda) which was similarly hydrogenolyzed to give 41% H-Tyr-D-Ala-Gly-Phe-Leu-R3 (III; R3 = NHAda). This in vitro was 2.13 times as potent as morphine-HCl in inhibiting the contraction of guinea pigs intestinal tract in the Kosterlitz's assay. Also prepared were III (R3 = OAda, OCH2Ada, OCH2CH2Ada), zidovudine derivs. (IV; R4 = AdaCO, etc.), and (adamantanecarbonyl)pyrrolidone.

IT **139143-34-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, with high blood-brain barrier permeability, for AIDS treatment)

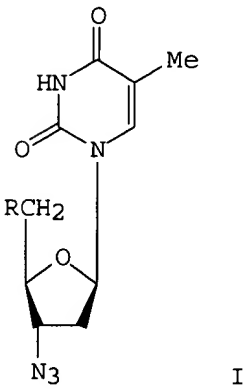
RN 139143-34-3 HCAPLUS

CN Glycine, N-(tricyclo[3.3.1.13,7]dec-1-ylcarbonyl)-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 33 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:129551 HCAPLUS
DOCUMENT NUMBER: 116:129551
TITLE: Lipidic peptides. IX. Synthesis and structural elucidation of lipophilic azidothymidine conjugates
AUTHOR(S): Hussain, Rohanah; Toth, Istvan; Gibbons, William A.
CORPORATE SOURCE: Sch. Pharm., Univ. London, London, WC1N 1AX, UK
SOURCE: Liebigs Annalen der Chemie (1992), (2), 169-71
CODEN: LACHDL; ISSN: 0170-2041
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

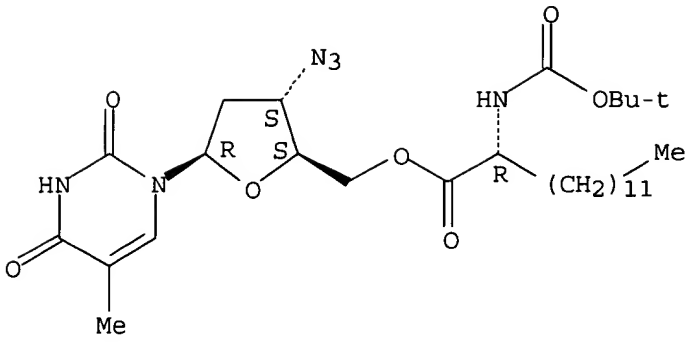
AB AZT conjugates with fatty amino acids and peptides I [R = Boc[NHCH[(CH2)11Me]CO]nNHCH[(CH2)mMe]CO2; Boc = Me3CO2C; n = 0-2, m = 11; n = 1, m = 9, 17] were prepared by coupling of AZT and the corresponding fatty amino acid or peptide with DCC. Sulfide conjugate I [R = Me(CH2)17S] was prepared from AZT tosylate I (R = 4-MeC6H4SO3).

IT **138089-87-9P 138089-88-0P 138089-89-1P**
138089-92-6P 138128-45-7P 138128-46-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 138089-87-9 HCAPLUS

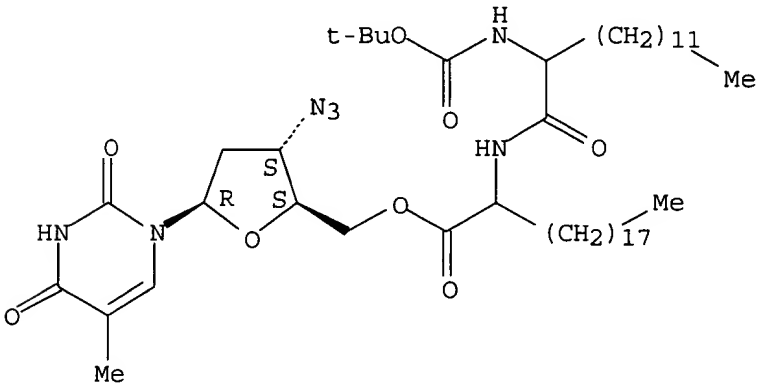
CN Thymidine, 3'-azido-3'-deoxy-, 5'-[2-[[(1,1-dimethylethoxy)carbonyl]amino] tetradecanoate], (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



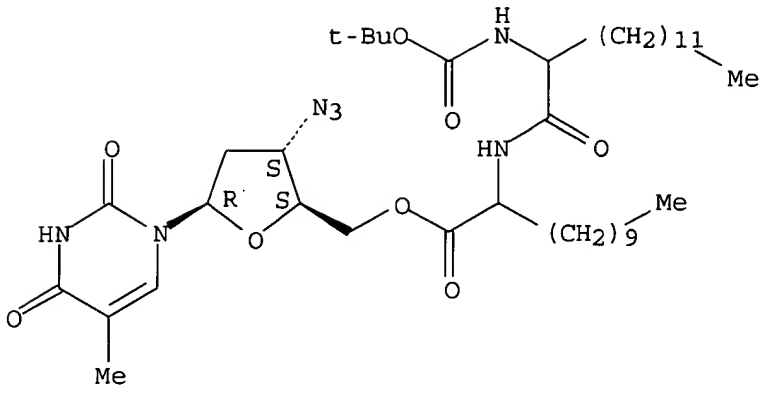
RN 138089-88-0 HCAPLUS
CN Thymidine, 3'-azido-3'-deoxy-, 5'-[2-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxotetradecyl]amino]eicosanoate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



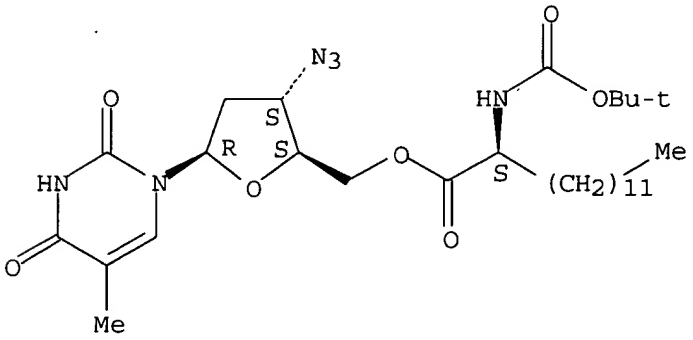
RN 138089-89-1 HCAPLUS
CN Thymidine, 3'-azido-3'-deoxy-, 5'-[2-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxotetradecyl]amino]dodecanoate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



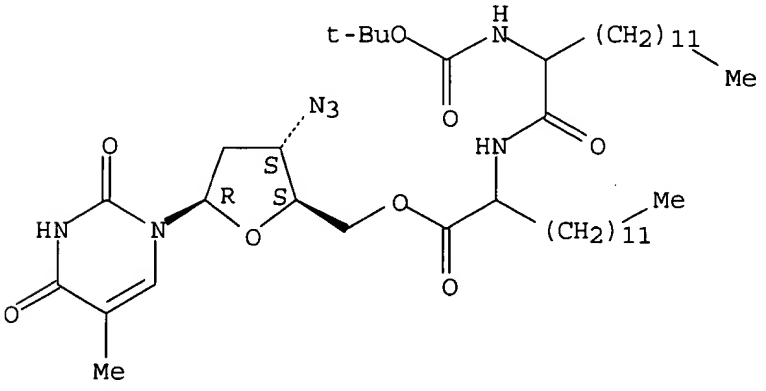
RN 138089-92-6 HCAPLUS
CN Thymidine, 3'-azido-3'-deoxy-, 5'-[2-[[(1,1-dimethylethoxy)carbonyl]amino] tetradecanoate], (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



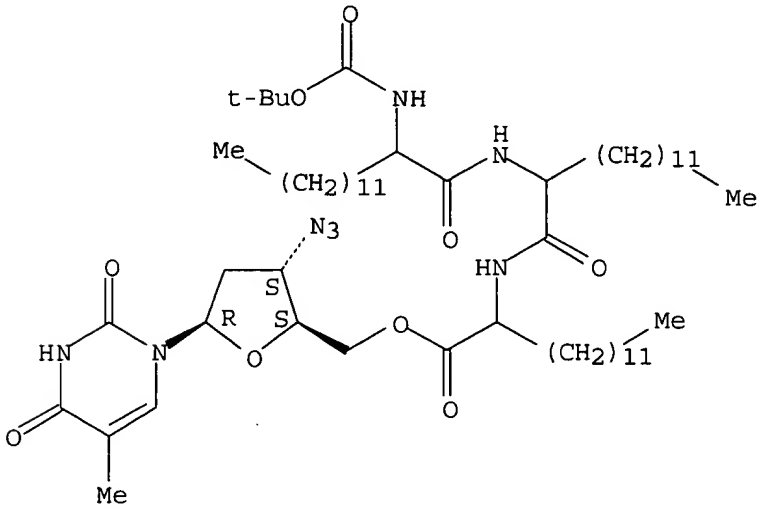
RN 138128-45-7 HCAPLUS
CN Thymidine, 3'-azido-3'-deoxy-, 5'-[2-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxotetradecyl]amino]tetradecanoate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.

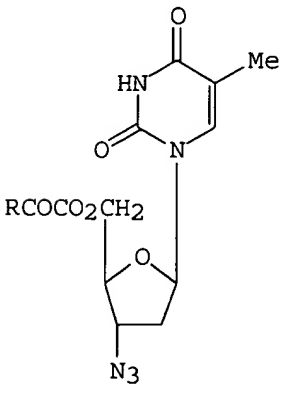


RN 138128-46-8 HCAPLUS
CN Thymidine, 3'-azido-3'-deoxy-, 5'-(2,5,8-tridodecyl-12,12-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatridecanoate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 34 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:106776 HCAPLUS
DOCUMENT NUMBER: 116:106776
TITLE: Synthesis of the 2',3'-dideoxynucleoside derivatives of the specific binding peptide part of CD4
AUTHOR(S): Uchiyama, Taketo; Yoshino, Hiroko; Takemoto, Masumi; Achiwa, Kazuo
CORPORATE SOURCE: Sch. Pharm. Sci., Univ. Shizuoka, Shizuoka, 422, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1991), 39(11), 3091-3
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

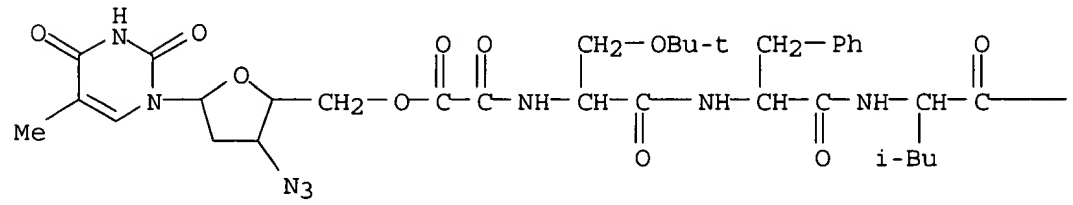
AB 2',3'-Dideoxynucleoside derivs., e.g. I (R = Pro-D-Phe-OCH2Ph, Ser-Phe-Leu-Thr-Lys-Gly-Pro-Ser-CH) of the specific binding peptide part of CD4 to HIV envelope protein gp120 were synthesized as potential HIV inhibitors.

IT **139300-59-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and deblocking of, with trifluoroacetic acid)

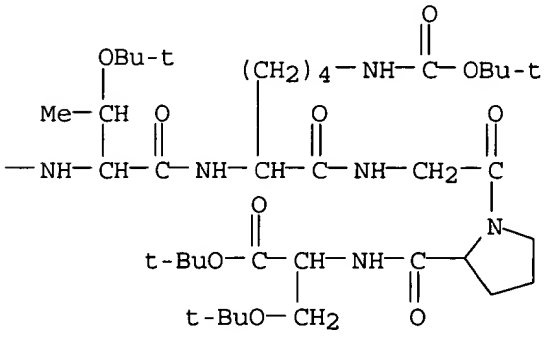
RN 139300-59-7 HCAPLUS

CN L-Serine, N-[1-[N-[N2-[N-[N-[N-[N-(carboxycarbonyl)-O-(1,1-dimethylethyl)-L-seryl]-L-phenylalanyl]-L-leucyl]-O-(1,1-dimethylethyl)-L-threonyl]-N6-[(1,1-dimethylethoxy)carbonyl]-L-lysyl]glycyl]-L-prolyl]-O-(1,1-dimethylethyl)-, 1-(1,1-dimethylethyl) ester, N-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



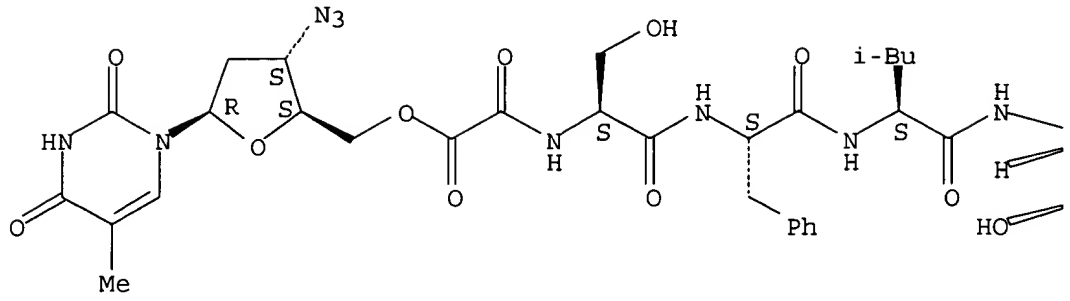
IT **139300-60-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 139300-60-0 HCAPLUS

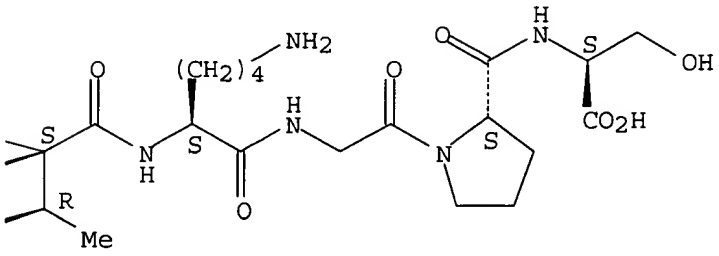
CN L-Serine, N-[1-[N-[N2-[N-[N-[N-[N-(carboxycarbonyl)-L-seryl]-L-phenylalanyl]-L-leucyl]-L-threonyl]-L-lysyl]glycyl]-L-prolyl]-, N-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L12 ANSWER 35 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:95145 HCAPLUS
DOCUMENT NUMBER: 114:95145
TITLE: AZT analogs for treatment of retrovirus infections
INVENTOR(S): Agrawall, Kirshna
PATENT ASSIGNEE(S): Tulane Educational Fund, Inc., USA
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9004969	A1	19900517	WO 1989-US4860		19891030
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE					
US 5026688	A	19910625	US 1988-265201		19881031
CA 2001899	AA	19900430	CA 1989-2001899		19891031
PRIORITY APPLN. INFO.:			US 1988-265201	A	19881031

OTHER SOURCE(S): MARPAT 114:95145
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

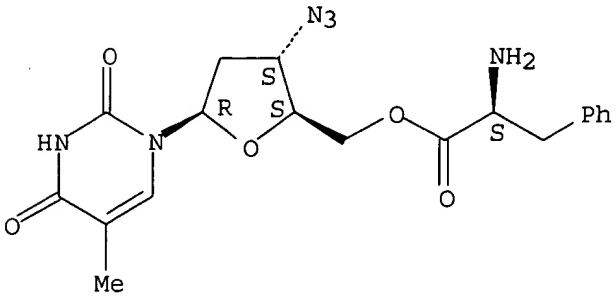
AB AZT analogs I (R = Q1, Q2, Q3; X = H, CO2H, C1-6 alkyl, PhCH2; Y = C1-6 alkyl, C6-10 aryl) are used for the treatment of retroviral infection.

Thus, II (preparation described) inhibited human immunodeficiency virus 1 replication 99.1% in vitro at 0.5 μM, vs. 82.0% for AZT. Toxicity data for II are also presented.

IT **125780-79-2 125780-81-6**
RL: BIOL (Biological study)
(retrovirus infection treatment with)

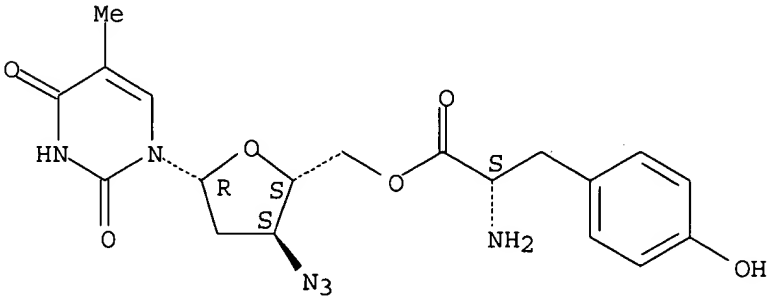
RN 125780-79-2 HCAPLUS
CN L-Phenylalanine, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 125780-81-6 HCAPLUS
CN L-Tyrosine, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

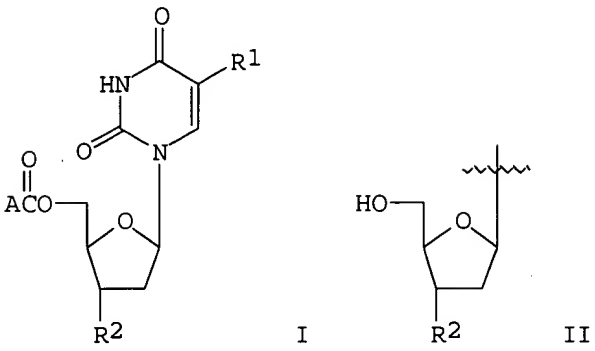
Absolute stereochemistry.



L12 ANSWER 36 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:459785 HCAPLUS
DOCUMENT NUMBER: 113:59785
TITLE: 3'-Azido-3'-deoxythymidine (AZT) derivatives active against the AIDS virus
INVENTOR(S): De Bethune, Marie Pierre; De Clercq, Erik Desire Alice; Dejonghe, Jean Paul; Pauwels, Rudi Wilfried Jan; Trouet, Andre
PATENT ASSIGNEE(S): IRE-Celltarg S. A., Belg.
SOURCE: Eur. Pat. Appl., 32 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 357495	A2	19900307	EP 1989-402340	19890824
EP 357495	A3	19910123		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
FR 2635778	A1	19900302	FR 1988-11284	19880826
JP 02083392	A2	19900323	JP 1989-221407	19890828
PRIORITY APPLN. INFO.:			FR 1988-11284 A	19880826
OTHER SOURCE(S):	CASREACT 113:59785; MARPAT 113:59785			

GI



I II

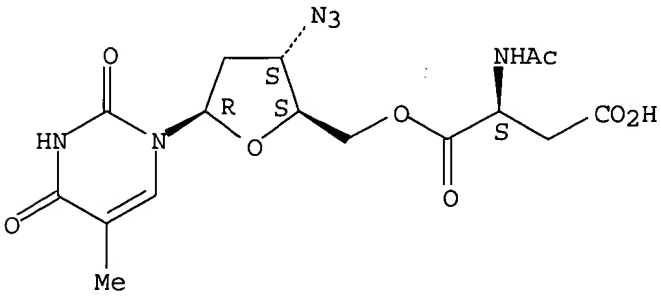
AB The title compds. [I; R1 = H, alkyl, alkoxy, hydroxyalkyl, halo; R2 = N3, cyano; A = (substituted) hydrocarbyl, etc.] were prepared by esterification of the hydroxy compds. II with ACO2H or their reactive derivs. Thus, acylation of 3'-azido-3'-deoxythymidine with succinic anhydride in pyridine gave I (R1 = Me, R2 = N3, A = HO2CCH2CH2) (III). The protective effect of III at 0.0004-5 μM concns. of HOT-/8 cells against HIV was comparable to that of AZT.

IT **128305-53-3P 128305-56-6P 128305-57-7P**
128305-59-9P 128305-60-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of, as antiviral)

RN 128305-53-3 HCAPLUS

CN L-Aspartic acid, N-acetyl-, 1→5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

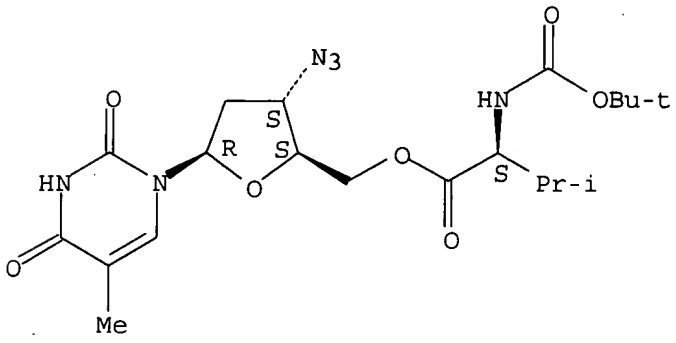
Absolute stereochemistry.



RN 128305-56-6 HCAPLUS

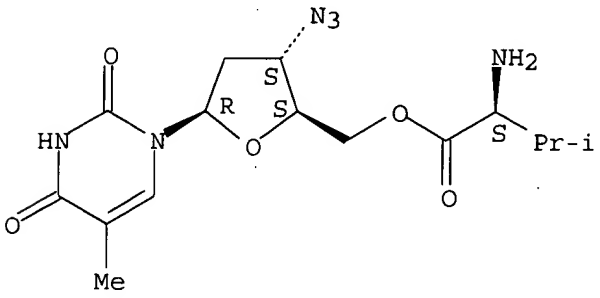
CN L-Valine, N-[(1,1-dimethylethoxy)carbonyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



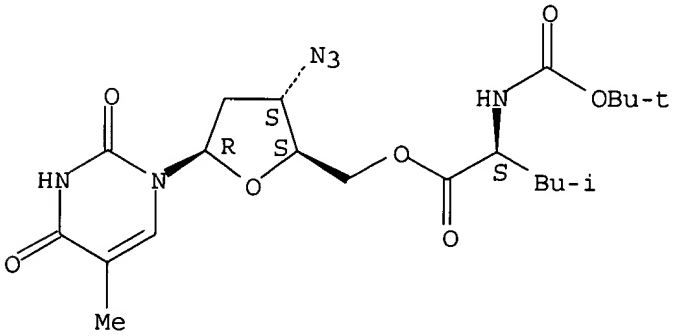
RN 128305-57-7 HCAPLUS
CN L-Valine, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



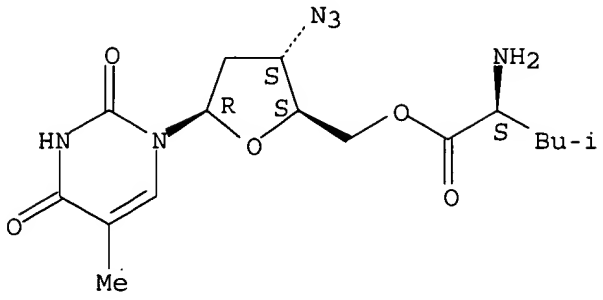
RN 128305-59-9 HCAPLUS
CN L-Leucine, N-[(1,1-dimethylethoxy)carbonyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

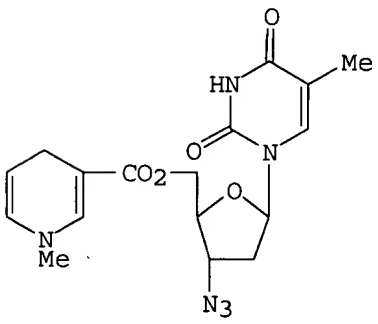


RN 128305-60-2 HCAPLUS
CN L-Leucine, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 37 OF 37 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:198959 HCAPLUS
DOCUMENT NUMBER: 112:198959
TITLE: Synthesis and biological evaluation of prodrugs of zidovudine
AUTHOR(S): Aggarwal, Sunil K.; Gogu, Sudhir R.; Rangan, S. R. S.; Agrawal, Krishna C.
CORPORATE SOURCE: Sch. Med., Tulane Univ., New Orleans, LA, 70112, USA
SOURCE: Journal of Medicinal Chemistry (1990), 33(5), 1505-10
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 112:198959
GI



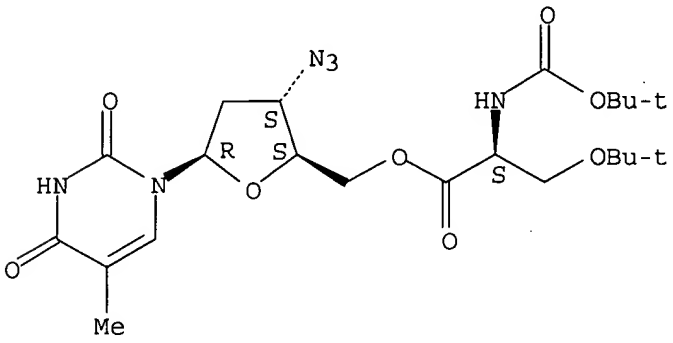
I

AB A series of prodrugs of zidovudine (AZT) was synthesized in an effort to enhance the uptake of the prodrugs by the HIV-1 infected cells and to increase the plasma half-life of AZT. The 5'-OH function of AZT was esterified with various acids in the presence of DCC and 4-(dimethylamino)pyridine (DMAP). The prodrug moieties included (a) morpholine and N-phenylpiperazine-1-acetic acid, (b) 1,4-dihydro-1-methyl-3-nicotinic acid, (c) retinoic acid, and (d) certain amino acids. The anti-HIV-1 activity of the esters was determined in peripheral blood lymphocytes. The IC50 for AZT in this system was 0.12 μM whereas for prodrugs it ranged from 0.05 to 0.2 μM. The prodrugs were generally less cytotoxic than AZT except the retinoic acid ester. In vitro hydrolysis of the various esters in human plasma indicated that these agents were relatively stable toward plasma esterases with t1/2 ranging from 10 to 240 min. Drug uptake studies in H9 cells with radiolabeled

analogs demonstrated that the retinoic acid ester achieved approx. 4-fold higher intracellular concentration than [3H]AZT. However, dihydromethylpyridylcarbonyl ester (I) was the most active agent of this series and had a higher therapeutic index than AZT.

IT **125780-78-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and attempted debutoxycarbonylation of)
RN 125780-78-1 HCAPLUS
CN L-Serine, N-[(1,1-dimethylethoxy)carbonyl]-O-(1,1-dimethylethyl)-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

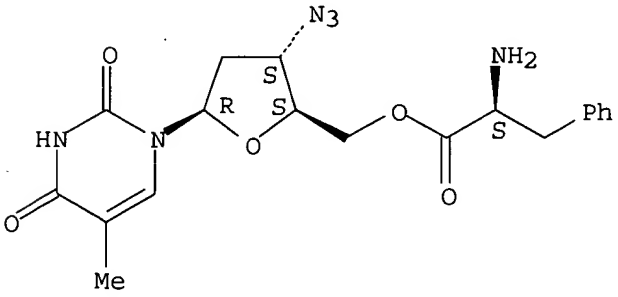


IT **125780-80-5P 125780-82-7P 125780-84-9P**
125780-86-1P 125780-96-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and bioactivity of)
RN 125780-80-5 HCAPLUS
CN L-Phenylalanine, 5'-ester with 3'-azido-3'-deoxythymidine, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

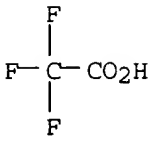
CRN 125780-79-2
CMF C19 H22 N6 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

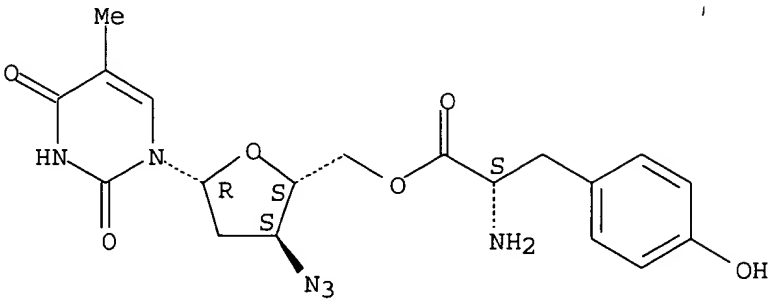


RN 125780-82-7 HCAPLUS
CN L-Tyrosine, 5'-ester with 3'-azido-3'-deoxythymidine, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

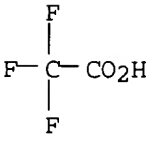
CRN 125780-81-6
CMF C19 H22 N6 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

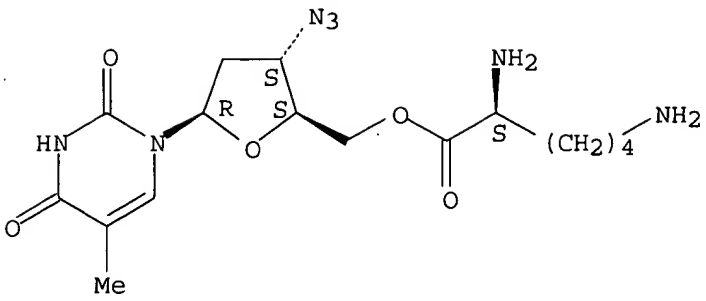


RN 125780-84-9 HCAPLUS
CN L-Lysine, 5'-ester with 3'-azido-3'-deoxythymidine, bis(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

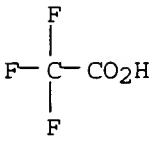
CRN 125780-83-8
CMF C16 H25 N7 O5

Absolute stereochemistry.



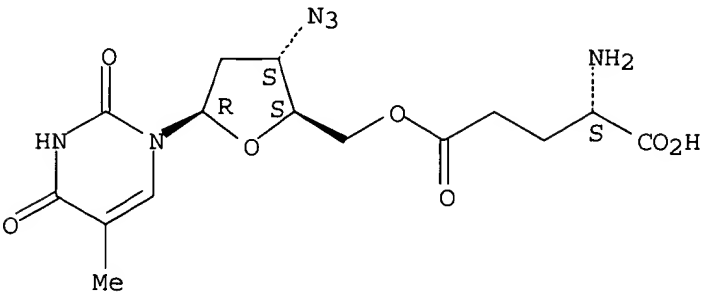
CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 125780-86-1 HCAPLUS
CN L-Glutamic acid, 5→5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

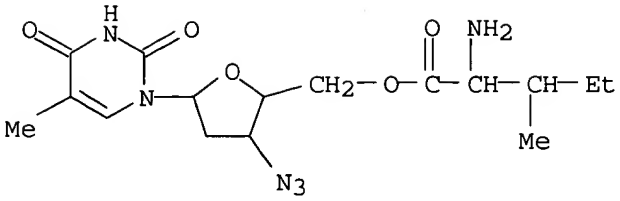
Absolute stereochemistry.



RN 125780-96-3 HCAPLUS
CN L-Isoleucine, 5'-ester with 3'-azido-3'-deoxythymidine, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

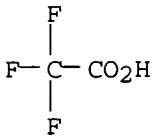
CM 1

CRN 125780-95-2
CMF C16 H24 N6 O5



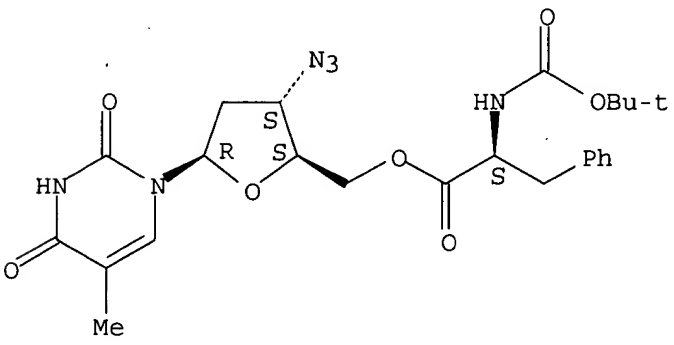
CM 2

CRN 76-05-1
CMF C2 H F3 O2



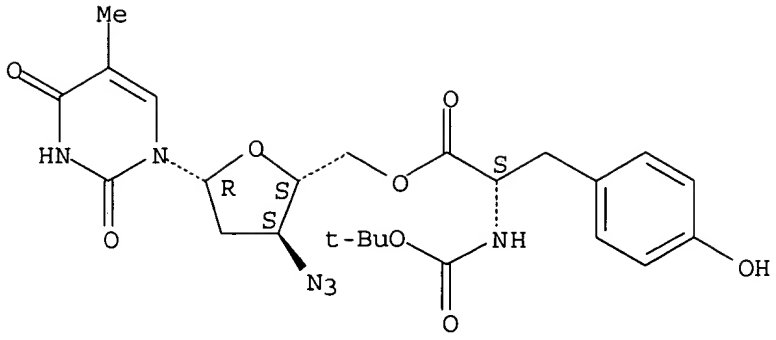
IT **125780-75-8P 125780-76-9P 125780-77-0P**
125780-85-0P 125780-98-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and debutoxycarbonylation of)
RN 125780-75-8 HCAPLUS
CN L-Phenylalanine, N-[(1,1-dimethylethoxy)carbonyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



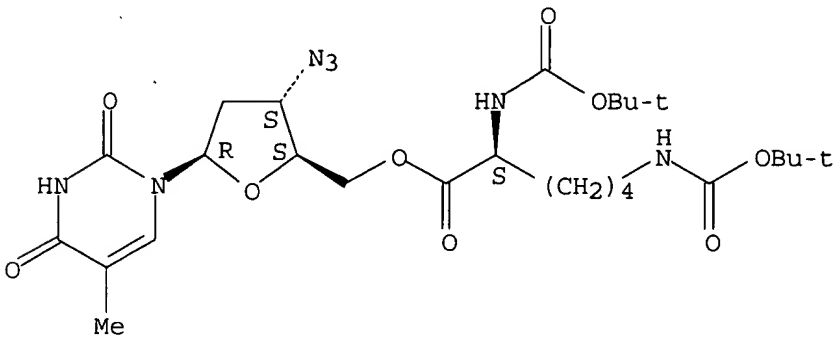
RN 125780-76-9 HCAPLUS
CN L-Tyrosine, N-[(1,1-dimethylethoxy)carbonyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



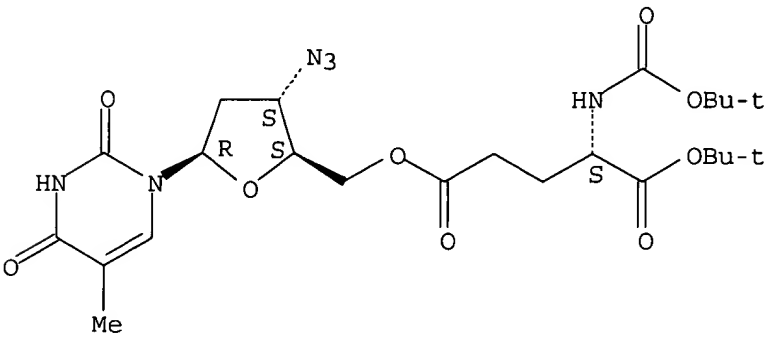
RN 125780-77-0 HCAPLUS
CN L-Lysine, N2,N6-bis[(1,1-dimethylethoxy)carbonyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 125780-85-0 HCAPLUS
CN L-Glutamic acid, N-[(1,1-dimethylethoxy)carbonyl]-, 1-(1,1-dimethylethyl) ester, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 125780-98-5 HCAPLUS
CN L-Isoleucine, N-[(1,1-dimethylethoxy)carbonyl]-, 5'-ester with 3'-azido-3'-deoxythymidine (9CI) (CA INDEX NAME)